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BULLETIN

OF THE NEW YORK ACADEMY OF MEDICINE

Original Articles by

GILBERT DALLDORF

GABRIEL GENKINS ISADORE KREEL
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THE RADIATION HAZARD
Transcription of a Panel Meeting

J. E. BALL TH. DOBZHANSKY
LOUIS H. HEMPELMANN, JR. JOHN S. LAUGHLIN
RUSSELL H. MORGAN

REPORT ON ADOPTIONS
COMMITTEE ON PUBLIC HEALTH

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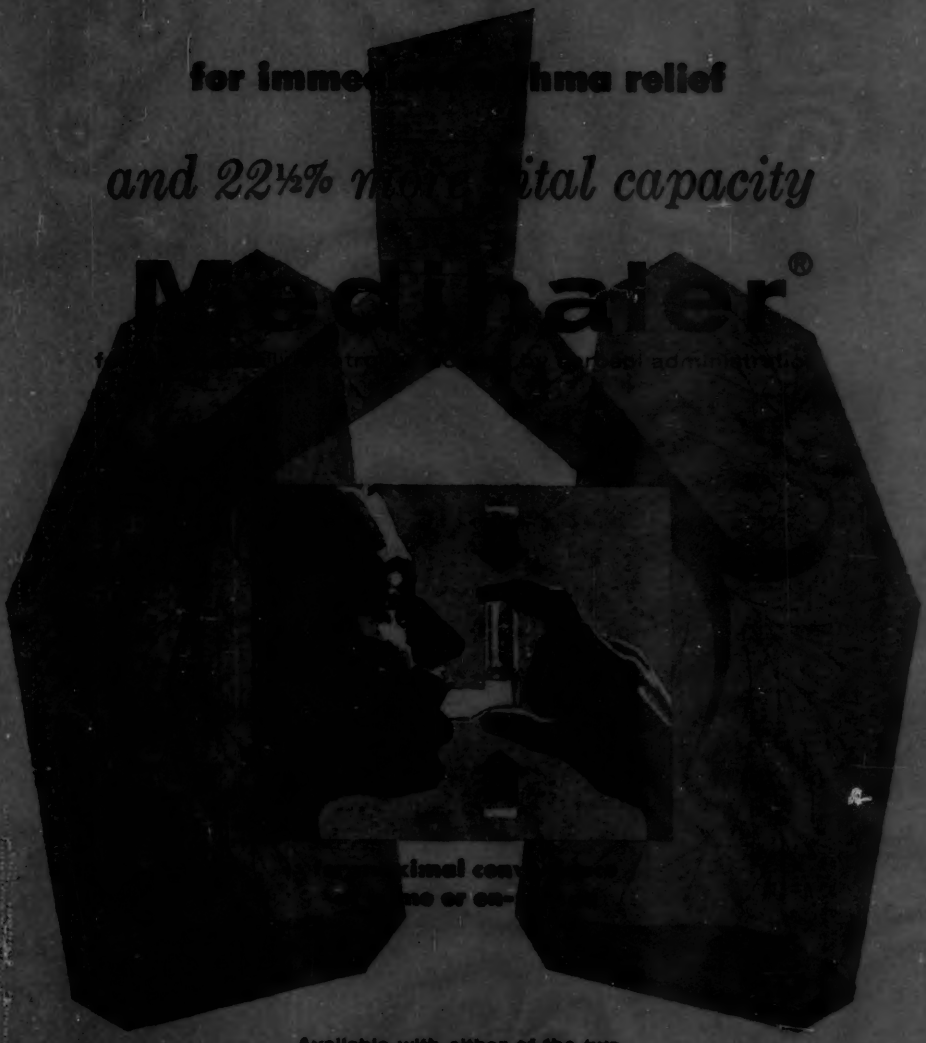

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1. Cameron, E.: The Use of Tofrānil in the Aged, Canad. Psychiat. A. J. Special Supplement, **4**:S169, 1959. 2. Christe, P.: Indications for Tofrānil in Geriatrics, Schweiz. med. Wchnschr. **90**:586, 1960. 3. Schmied, J., and Ziegler, A.: Tofrānil in Geriatrics, Praxis **49**:472, 1960.

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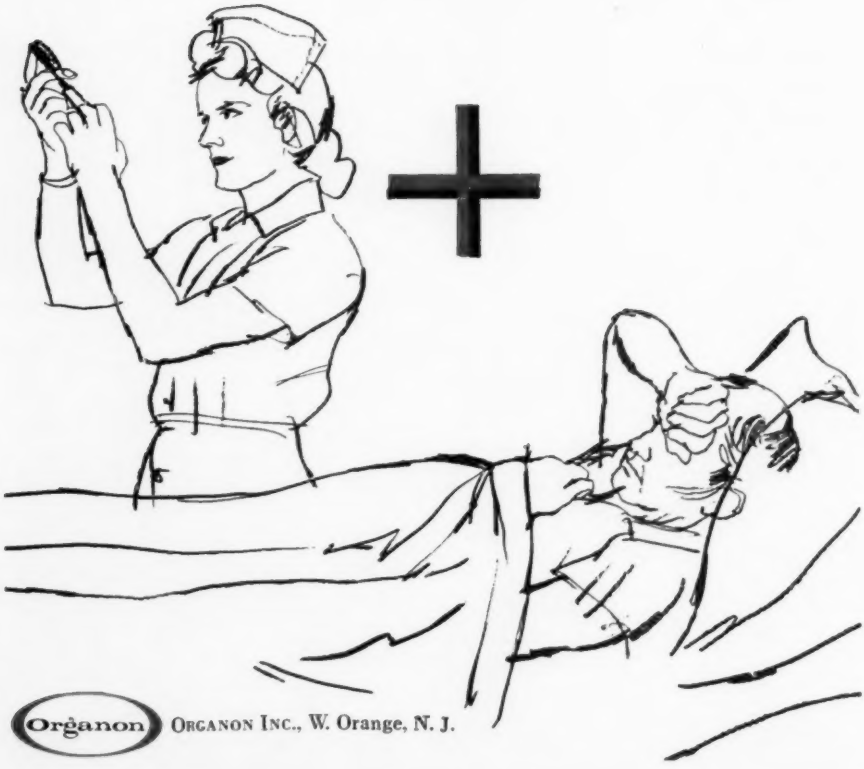

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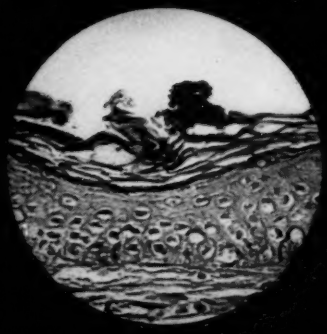

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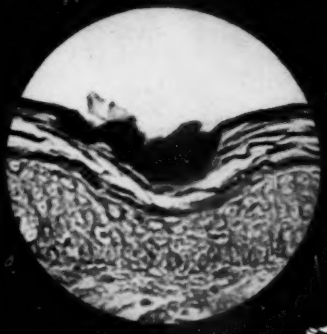

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1. Spoor, H. J.: New York St. J. M. 60:2863, 1960.
2. Wiese, H. F., et al.: J. Nutrition 66:345, 1958.
3. Smith, L. W., et al.: Amer. J. Med. Sc. 237:600, 1959.
4. Nutrition Reviews 17:136, 1959.

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*Zimmerman, F. T., & Burgemeister, B. B.: Neurology 8:769, 1958.

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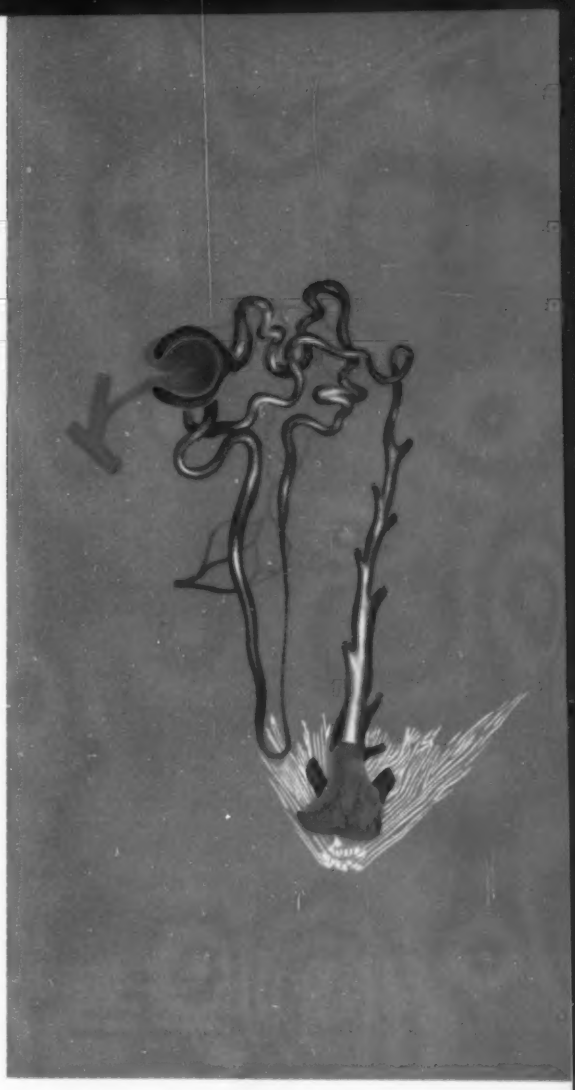

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References: 1. Schreiner, G. E.: A.M.A. Arch. Int. M. **102**:32, 1958. 2. Freedman, L. R., and Beeson, P. B.: Yale J. Biol. & Med. **30**:406, 1958. 3. Rocha, H., et al.: Yale J. Biol. & Med. **30**:341, 1958.

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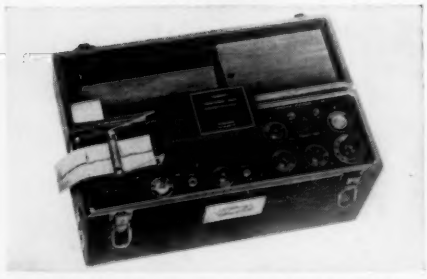

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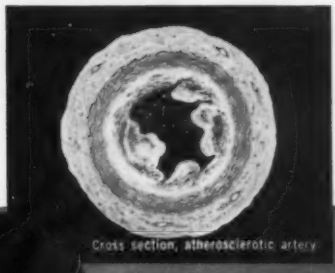
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Tracheobronchitis	32	23	4	3	2
Croup	14	10	2	2	0
Pleurisy	12	11	0	1	0
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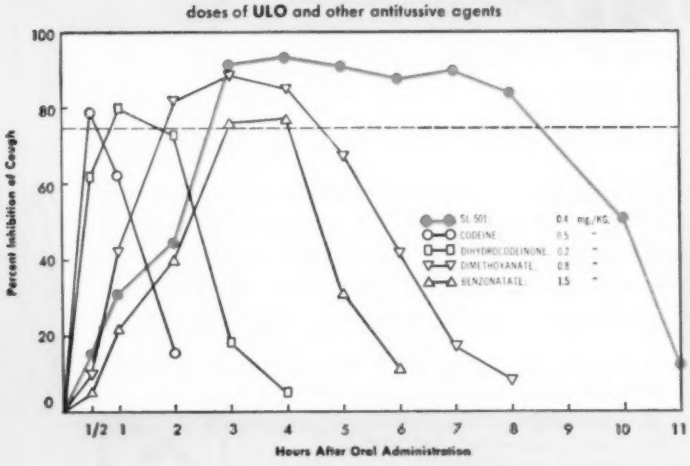

Mean per cent inhibition of cough in dogs following oral administration of therapeutically equivalent doses of ULO (SL-501) and other antitussive agents. The horizontal dotted line represents threshold of maximum effectiveness, arbitrarily taken at 75 per cent suppression of counted coughs. Note that the duration of maximum effectiveness of a single dose of ULO is 6 hours, 24 times as long as that of codeine. Peak effectiveness of ULO is not reached until 2 or 3 hours after administration, but the maximum antitussive action lasts at least 6 hours.

Chen, J. Y.; Biller, H. F., and Montgomery, E. G., Jr.: J. Pharmacol. & Exper. Therap. *128*:384, 1960.

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1. Stephens, V. C., *et al.*: J. Am. Pharm. A. (Scient. Ed.), *48*:620, 1959.
2. Salitsky, S., *et al.*: Antibiotics Annual, p. 893, 1959-1960.
3. Reichelderfer, T. E., *et al.*: Antibiotics Annual, p. 899, 1959-1960.
4. Kuder, H. V.: Clin. Pharmacol. & Therap., in press.

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AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

ROBERT L. CRAIG, *Editor*

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BULLETIN OF
THE NEW YORK ACADEMY
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VOL. 36, NO. 12 DECEMBER 1960

VIRUSES AND HUMAN CANCER*

GILBERT DALLDORF

Walker Laboratory, Sloan-Kettering Institute, Rye, New York

THE remarkably fine studies of polyoma virus by Dr. Eddy and her colleagues have whetted interest in the possible role of viruses in human cancer. If polyoma virus infection proves to be a model of a disease of man, think of the medical opportunities: simple tests of infection, past and present, immunization and prospects of control by quarantine or otherwise breaking the cycle of infection. It is new knowledge of the kind Dr. Eddy has reported, coupled with the advances in protein chemistry and genetics, that shows how well alien, exogenous nucleic acids, as from viruses, could account for the malignant transformation of cells, and that further spurs the search for human cancer viruses.

Unfortunately I cannot tell you about such a virus. But I can describe a rather unusual virus that we have found in transplanted human cancers. Whether it causes cancer or is only associated with it, I do not know. It has drawn my attention to the great difficulty of recognizing a cancer virus and of proving that a suspect is in fact the cause of cancer.

From a theoretical standpoint one might consider whether some of our common, familiar viruses cause cancer. If what has been learned

* Presented at a meeting of the New York Cancer Society at The New York Academy of Medicine, October 11, 1960.

about the transformation of bacteria and viruses and cells by foreign nucleic acids is applicable to neoplastic diseases, we should certainly consider the possibility that common viruses, following sojourn in cancer, can acquire malignant markers which they could transmit to other hosts. This would be an example of transduction, a well-established phenomenon of bacteria. I don't know how one would undertake to tackle that problem, but it illustrates the difficulties we face. And our newly recognized agent poses the question very directly.

The new virus, which might be described as an osteolytic virus, is found in human cancers adapted to and transplantable in laboratory animals. Many of you are acquainted with Dr. Toolan's achievements in propagating various cancers in hamsters, which have provided oncologists with a permanent supply of human cancer cells. During studies of the immunologic relationship between these tumors and their hamster hosts, Toolan observed that hamsters which had been inoculated with fractions of transplantable cancers when newborn, frequently became deformed.[1] It is a striking deformity characterized by flat face, exophthalmos, protruding tongue, general stunting, and abnormal teeth. It has been spoken of as mongoloid. These hamsters remind one of human mongolism.

The property of causing this remarkable deformity was found in all eight of the transplantable human cancers. The greatest activity was in the endoplasmic reticulum fraction of the cells. The active principle was stable in the cold, destroyed by heat, was readily filterable, and very potent. Minute doses sufficed to induce the deformity. Toolan learned a great deal more about the disease. If the mongoloid animals were bred, their young were quite normal. It was evidently not hereditary. The organs of the deformed animals were not remarkable, their endocrine glands were not significantly affected. Iodine uptake was normal. The tissues were not infectious.

Despite the lack of evidence of infectivity, the possibility of a viral nature was not abandoned, and Toolan and I have now found the virus that is responsible.[2] While the tissues of the mongoloid animals are not infectious, this is only true of the time when the deformity may be recognized, usually about two weeks after inoculation. Tissues harvested a week earlier are highly infectious, and if the infection is rapidly transferred through groups of hamsters, the titer of the virus, and presumably its virulence, rapidly increase. After one or more

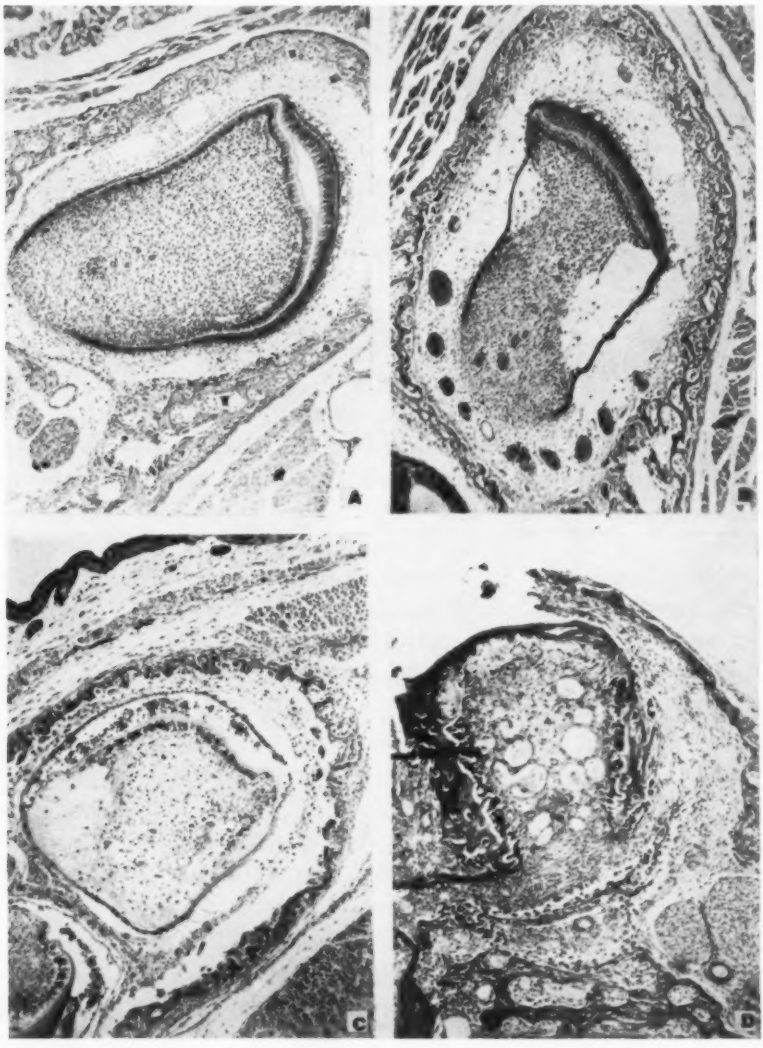

Figure 1. Sequences in hamster incisor following infection with the osteolytic virus.

A. is a normal incisor.

B. is a typical early lesion consisting of necrosis of odontoblasts and cystic degeneration of the adjacent pulp.

C. is a more severe stage of the acute lesion.

D. is a later stage (9th day) in which the intercellular material resembles bone rather than dentine.

passages, the usual outcome is death of the animals within the first week of life, before the deformity is manifest.

This has led to an improvement in the isolation of the virus. At present one or two blind passages are made to permit adaptation. We do not yet know how much more sensitive this procedure is, but the earlier results may need to be amended on the basis of the newer technic.

The pathogenesis of the mongoloid deformity, as well as its cause, became clear when the early stages of the infection were studied histologically. We have found that the morbid effects are principally in the bones and teeth. In this respect the new virus seems to be unique among all known viruses. There are initial changes in the liver, largely in the Kupffer cells, and presumably in the reticuloendothelial system generally, but these structures are a common target of viruses, and the lesions are little if at all different from those in other infections.

The lesions of the teeth and bones, on the other hand, are distinctive and rather remarkable. The incisors are an especially satisfactory structure in which to follow the sequences. Within a few days changes occur in the pulp with degeneration of odontoblasts and cystic necrosis of the supporting stroma and about the tooth in the tooth socket. These are both degenerative and inflammatory, but are relatively free of exudative cells. The process develops very rapidly. During the second week, the tooth may be completely destroyed or the dentine may become abnormal, at times resembling bone more than dentine (Fig. 1).

The effects of these lesions are, of course, evident in the living animal. One or more teeth may be lacking or be thin, twisted, and discolored. Indeed, the appearance of the teeth is quite as useful in identifying the disease in the living animal as the histologic study has been in exploring its pathogenesis.

The lesions of the bones are equally striking. The flat bones of the skull are much affected. The osteoblasts degenerate or die, and after a week remnants of dead bone are found that correspond with the defects of the facial bones that cause the deformity. The mandible and long bones show remarkable changes, especially near their growing ends. At the costochondral junctions the osteoblasts deteriorate and sometimes assume spindle or stellate forms (or are replaced by such cells). At times there is a broad zone of such abnormal cells across the junction of cartilage and growing bone that somewhat resembles the *gerüstmark* one sees in scurvy (Figure 2). Abnormally staining and

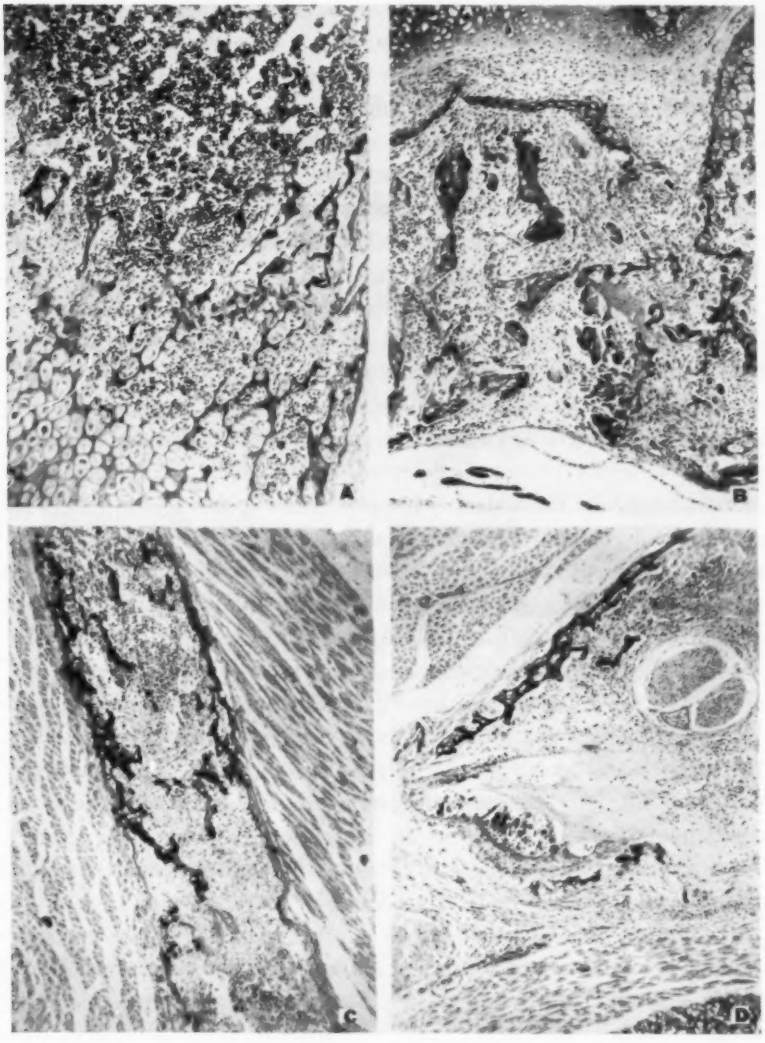

Figure 2. Three representative skeletal lesions in immature hamsters following infection with the osteolytic virus.

A. shows a portion of a costochondral junction in which masses of abnormal osteoid material and a zone of stellate and spindle-shaped cells may be seen, which somewhat resembles the "gerüstmark" of scurvy.

B. represents an area of collapse with repair by abnormal intercellular material.

C. is of a bone that is largely necrotic and much of which has been resorbed.

D. is a late lesion of a tooth that has been largely destroyed with the cancellous bone supporting it.

presumably inferior intercellular material may be deposited, and bony fractures and collapse are not uncommon. It is hardly surprising, therefore, that we have found the bones themselves to be highly infectious.

The deformity is the consequence of the disease, not the disease itself. The disease is an acute one with a brief incubation period that is caused by a virus with a unique tropism for bones and teeth. These structures may be so severely damaged that they never completely recover. The results are skeletal and dental defects that become more obvious with the growth of the animal.

The virus has not yet been measured by filtration, but infectious preparations contain many particles of approximately 70 mμ diameter. And a few observations of infected tissues have also disclosed particles of that size. In the cells they have been found in small cytoplasmic vesicles, and some have contained a small nucleoid. They are morphologically different from other viruses with which I am acquainted.

As I have said, the virus has been recoverable at will from all of the transplantable human cancers we have tested. It has not been isolated from normal hamster tissues or from a number of transplantable animal tumors, the Crocker sarcoma 180, Ehrlich carcinoma (both of these were in the ascitic form), the Bashford carcinoma, and Glioma 26. Nor was virus found in three spontaneous mammary tumors of Swiss mice. The Jensen rat sarcoma and the Walker rat carcinosarcoma also gave negative results. Four human tumors that have been propagated *in vitro*, HEP 1 and 2, HELA and HS 1, were noninfectious, but this may be due to the long exposure to horse and calf sera which these cells experience during their artificial cultivation. The virus apparently propagates in explants of infected hamster spleen and possibly in other cells *in vitro*.

A number of isolations have been made from the tissues of cancer patients, while their tumors have, so far, not been infectious. In this regard I should mention that the livers and spleens and, to a lesser extent, the brains of rats carrying the transplanted human cancers have been as infectious as the tumors themselves. All of these observations require much more attention. There is, indeed, so much to be done that I hope others will be tempted to take a hand.

Whatever the future may teach us about this osteolytic virus, it seems quite clear to me that it raises the question of how we may hope to recognize a human cancer virus (if we find one) in a very direct and

unavoidable way. For we now are faced with a very real virus that is evidently uniformly present in all of our transplanted human cancers. Surely we are obliged to determine, if we can, whether it plays an important role or is only a passenger.

The problem of establishing the etiologic importance of bacteria and viruses has often been troublesome. It was troublesome in the early days of bacteriology and was discussed at length by Koch at the Tenth International Medical Congress in Berlin in 1890.[3] Subsequently extracted from his lecture are four criteria that have since become known as Koch's postulates. Koch did not formulate them as such, although he gave great weight to them. The postulates require that the agent be regularly demonstrable in patients ill with the disease, be cultivated in pure form *in vitro*, demonstrated to be capable of reproducing the disease in experimental animals and, finally, be recovered from the experimental host.

These requirements were admirably suited to tuberculosis, with which Koch had been working. They were of little value to virologists who have never grown viruses in sterile, lifeless media, and who often find that viruses induce lesions in experimental animals that seem to bear little resemblance to the lesions of the naturally occurring disease. So virologists learned to rely on demonstrating that, coincidental with the appearance of a particular virus in a particular illness, the patient developed antibodies for that virus. Koch's work antedated the discovery of antibodies, and I do not doubt he would have appreciated the significance of antibodies, had he known about them.

He did, however, have other things to say in his lecture. For example, he made much of the significance of isolations of the pathogen from the lesions. He noted the importance of isolating typhoid bacilli from the spleen. And he was fully aware of the necessity of modifying his criteria to meet special situations.

In the case of cancer viruses, we may hope to find substantial evidence in the regularity with which they are associated with cancer or perhaps certain types of cancer, Koch's first postulate. We cannot hope to cultivate them free of the risk of latent viruses, whether we use animals or cultured cells. I suspect that the prospects are not good that a human cancer virus, if such exists, will readily induce the same tumor in lower animals. The significance of antibodies is also worrisome, for we know very little of the precise onset of cancer and suspect that it is

a late effect, often following by many years the exposure to the causative agent. Yet this possibility deserves thorough examination.

Certainly no deliberate attempt to test candidate viruses in man should be considered; and here Dr. Eddy and her associates have had an enormous advantage. Without such evidence, can we ever be certain?

I doubt that the inability of the osteolytic virus to induce tumors in the hamsters is significant. It is commonplace, in virology, to find that viruses cause quite different responses in different hosts. Influenza virus infection of chick embryos bears no resemblance to human influenza. Moreover, it has been known for twenty years that some animal tumor viruses cause host responses apparently unrelated to the tumors associated with them in nature. This is true of the chicken sarcoma and rabbit fibroma viruses when they are inoculated into newborn animals.[4] Age apparently determines the character of the response.

Despite these and other difficulties, I think the prospects are not quite so dark as they may seem to be. In the case of the hamster virus I have described, and which forces us to face the problem so directly at this time, we have other possible avenues of study. It would certainly mean a good deal if we find antibodies more or less consistently in patients with, perhaps, particular kinds of cancers. It would also be significant if they were never, or perhaps only rarely, present in man. It is quite possible that another source of the hamster virus will be discovered than the human tumors, and the decision will thus be established in reverse. We have made very earnest efforts to exclude the possibility that the virus has been picked up from hamsters, in whom it may possibly occur in a latent form. The negative controls have seemed to me to furnish the critical aspect of these early stages of the work. It nevertheless is possible, in view of what is known of other virus diseases, that the latency, in hamsters, is sufficiently obscure to make our present tests inadequate.

And finally, I have learned to expect that new unsuspected opportunities frequently arise. During the exploratory years of the Coxsackie viruses, questions of this kind, but now, in retrospect, never quite so formidable, often arose. It was obvious, for example, that the relative ubiquitousness of the Coxsackie viruses made proof of causal relationships especially difficult. One suggestion made at the time was that the specific virus types not only be found with regularity in typical cases of the suspect illness, but that they NOT be found, to a

comparable degree, in equivalent numbers of appropriate controls. Reliance should be placed on critical statistical analyses of the results in both groups.

Not long afterward, Dr. James Gear implicated Group B Coxsackie viruses as the etiologic agent of a form of severe myocarditis that sometimes occurs in newborn infants.[5] He had very few cases. It is not a very common disease. But the association seemed obvious to him, and his judgment has been confirmed by many subsequent experiences. The etiologic role of Group B Coxsackie viruses in the myocarditis of infants is now as firmly established as the role of certain Group A viruses in herpangina, which was thought to require special degrees of proof. What had been recommended in respect to herpangina would have been impossible in the case of epidemic myocarditis neonatorum. Interestingly, Gear found the virus in the heart muscle, which Koch would have appreciated, and he also showed that the mothers of these infants frequently had epidemic pleurodynia, which means Group B Coxsackie virus infection. The myocarditis always occurred when Group B viruses were epidemic. In other words, a good deal of evidence supported and was harmonious with his laboratory results.

It seems to me pretentious and arbitrary to attempt at this time to establish the criteria necessary to prove the carcinogenic nature of a virus. But we should think about it and seek the kind of evidence suitable to the problem. That, at any rate, is our immediate responsibility in the case of the hamster virus.

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THE RADIATION HAZARD

*Transcription of a Panel Meeting**

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MODERATOR J. E. RALL: This earth has been involved with radiation since before the origin of life on this planet and, for better or worse, radiation continues to be a part of our environment, perhaps to a greater degree now than in the past. As biological organisms we are constantly exposed to radiation and, of course, use it in many different forms. The physician employs it in diagnosis and therapy and, in one form or another, scientists resort to using it almost daily. Knowledge of its potentialities, favorable or unfavorable, is essential before relying upon it as a therapeutic adjunct.

In our panel discussion, the nature of radiation will be considered, how it is quantitated, its inherently damaging aspects and their cause and avoidance. In discussing our topic, the positive aspects of radiation are implicit in that it does not present an unmixed "hazard".

Without further ado, I shall now call on Dr. John S. Laughlin to discuss "Population Dosimetry".

DR. JOHN S. LAUGHLIN: By its very nature, dosimetry is expressed in numbers. Since, however, we are concerned with many different conditions—different kinds of radiation from a large variety of sources, exposure of different portions of the body, and also exposure of many different individuals to many different procedures—the use of numbers sometimes gives an illusory sense of accuracy. It must, therefore, be emphasized that, although it is necessary to use numbers when talking about dosage, it does not necessarily follow that there are no discrepancies associated with these numbers.

The two regions of the body to which dosimetry is primarily directed are: first, the gonads, with the gonadal dose being related to genetic injury; and second, the bone marrow, with the mean marrow dose having some relation to the incidence of leukemia and other aging processes in the body.

A distinction should be made between the average gonadal dose that a population might receive and the so-called genetically significant dose, because that part of the population receiving the gonadal dose may be quite different from the rest of the population. This refers specifically to those who receive medical x-ray exposure. Since the reproductive expectancy of individual patients is not known, certainly not with the precision that the reproductive expectation of the general population is known, there is an inherent difficulty in assessing the genetically significant dose. It is less difficult to determine the average

gonadal dose for the population.

Other effects to be considered with regard to the interpretation of these doses will, I am sure, be discussed later on. These refer to whether or not there are linear or threshold dependencies of these biological effects on dose.

As a base line reference, I should first like to say a few words about the natural background dose. Everyone is exposed unavoidably and inevitably to natural background radiation. Even though all other radiation sources are avoided, all of us receive some natural background radiation during every minute of our existence. This consists, in general, of three different parts. First, the portion of background radiation that comes from cosmic ray exposure; secondly, a portion that comes from the contamination of the earth's crust, including all building materials, which contain a large amount of radioactive material; and thirdly, our bodies contain radioactive material inherent in their constitution.

The term "cosmic rays" is a very general term which specifically refers to the charged heavy particles which enter the earth's atmosphere from outer space. These charged particles have energies of many billions of electron volts. They dissipate their energy in the earth's atmosphere, so that what reaches us is not the original positively charged particle. We receive the gamma rays, the mesons and the neutrons, which are created when the primary cosmic rays are absorbed in the earth's atmosphere. We are exposed continually to secondary cosmic rays.

(Slide) Here is indicated pictorially the gonadal dose due to cosmic rays which is approximately 30 millirads per year. I shall use the terms "millirad" and "millirem" interchangeably. For our purposes they will mean the same thing, and they also are equivalent to the milliroentgen. I think everyone is familiar with the roentgen unit, which is often used in x-ray dosimetry. In referring to the milliroentgen, or millirad or millirem, we are referring to a much smaller unit, one-thousandth of a roentgen; and the average annual background dose due to cosmic rays is a little less than 30 of these millirem each year. Since this is a highly penetrating radiation, it does not make any significant difference whether the gonadal dose or fingertip dose is considered; it is essentially the same throughout the body and will be equal to approximately 30 millirem per year at the altitude at which the average person resides.

The earth's crust contains large amounts of uranium, thorium, and

potassium, and all of us are continually being bombarded by gamma rays from these sources, whether we are outside or indoors. When we are indoors we receive some additional radiation from the material used in the construction of the building in which we happen to be. We also get some reduction in dose due to shielding, so that the internal dose received while inside the building depends considerably on the nature of the material used in constructing the building. The "hottest" places in which to live and work are made of concrete, since concrete often contains appreciable amounts of uranium. Brick comes next and, as far as radiation is concerned, living in a brick building would almost be equivalent to being outdoors. There have been instances of concrete dwellings with radiant heating in which the amount of radon gas driven out of the walls approached the so-called maximum permissible levels. This is an extremely rare occurence, however. This combination of earth and housing dose, together with the cosmic ray dose, adds up to approximately 75 to 80 milli-r per year. It should be noted that this is a rough average figure and will vary greatly depending upon the locality in which a person lives. If a person lives at the top of Pike's Peak, the cosmic ray contribution will be greater. The millirem there would be almost double that shown on the slide. There are certain areas in India where the sands are highly radioactive and the dose due to both cosmic rays and earth and housing rises to over 800 milli-r per year.

(Slide) The last major source of natural background radiation is internal radioactivity due to the amount of potassium and carbon and radium within the body. This is indicated here in millirem per year, with a total that is approximately equal to the cosmic ray contribution.

(Slide) This summarizes the figures seen on the preceding slide and indicates that for the gonadal dose the total per year per person is approximately 100 milli-r or 0.1 roentgen. If you consider the osteocyte dose, which would be the dose in bone, this is greater solely because of the contribution of the radium content of bone, which is normally present and brings the osteocyte dose up to approximately 130 milli-r. Possibly of more significance is the mean marrow dose, which is essentially equal to the gonadal dose. In addition to the natural background sources of radiation there are various man-made sources which have to be added on. These include any medical x-ray exposures, industrial x-ray exposure and weapons-testing exposure.

With regard to medical x-ray exposure, it is extremely difficult to assess the amount of radiation from this source because it varies greatly from person to person and because it is extremely difficult to accumulate significant statistics on this point. Also, the procedures employed are so varied that comprehensive measurements are necessary under difficult circumstances to determine the gonadal and marrow doses in medical procedures. However, on the basis of estimates made on reported measurements, the United Nations Committee has indicated that in some European countries the average gonadal dose is of the order of a quarter of natural background. In other countries the dose is probably higher, and in the United States there is supporting evidence to suggest that the minimal dose may be of the order of a half natural background, and sometimes may be as high as background. In some countries, where everyone who uses radiation is required to be a certified practitioner, it is much easier to determine what the dosage is. The lack of such restrictions in this country is the cause of difficulty in trying to arrive at a value for the United States.

(Slide) This is the data of one experimental result obtained for an ordinary chest radiograph which indicates that the bone marrow dose received from an exposure of an ordinary 14 x 17 film—and this is derived from measurements inside the bone in a phantom—was of the order of 15 milli-r, obviously very small, compared with the annual background dose. If this were done on a photofluorographic unit the dose would be about equal to the natural background dose.

(Slide) The other source of radiation is weapons-testing. The fallout on the earth's surface following weapons-testing generally arises from two different types of test, the megaton test which puts sizable amounts of fission products into the stratosphere, and the kiloton test, in which the radioactive material does not rise into the stratosphere but remains in the troposphere and falls on the earth during rain storms within a few months after the initial test. It has been estimated that about 90 per cent of the radiation received from weapons-testing is due to the megaton stratospheric radiation. We get the radiation, of course, only after the radioactive material has come down from the stratosphere and has fallen on the earth. The two isotopes which are of primary concern are strontium 90 and cesium 137, both of which have relatively long half-lives. As indicated here, the upper lines refer to natural background dose computed on a 30 year basis. One can see that a tenth of

a roentgen or 100 milli-r for 30 years produces a natural background dose of about 3 r in 30 years, which is a mean period of significance for genetic purposes.

The man-made dose, which would be primarily medical, is believed to be somewhere between a half roentgen and possibly up to 5. The occupational dose is as yet very small. The significance of this line is that if weapons-testing were to cease this year, the gonadal dose over a 30 year period due to radio-active material already in the stratosphere would amount to 1/100 roentgen or 10 milli-r, which is comparable to the natural background dose. If, however, weapons-testing is to be continued at the rate it has been proceeding during the last few years, the dose to the gonads would be of the order of 1/10 roentgen. Now in the case of the marrow dose, a 70 year figure is of greater significance, since this may be of importance throughout the entire lifetime, and in this case the natural background dose is seven roentgens. The man-made dose may be greater than seven on the average. The occupational dose also increases proportionately, and in this case the weapons-testing dose is of the order of .2 r, and for continuous testing may be of the order of 3 roentgens. I should mention that these figures, which are derived from strontium, are calculated on the basis of a milk diet. In Japan, where much of the calcium enters the body in the form of rice, it is believed this figure may be about six times higher.

MODERATOR RALL: This acquaints us with the numbers that must be of concern to us when we think about radiation.

There are certainly two major reasons for concern about radiation. One is the carcinogenic effects, which are well known and about which there is an ever-increasing amount of documentation, and the other is the genetic factor. *Dr. Hempelmann, our next speaker, will discuss his work in epidemiologic studies on the production of cancer by x-ray.*

DR. LOUIS H. HEMPELMANN, JR.: The aspect of radiation hazards that I wish to discuss concerns the malignant change which tissues sometimes undergo when subjected to ionizing radiations. For more than 50 years, x-rays and gamma rays have been known to cause cancer, following the first reported case of skin cancer in an x-ray worker in 1902. Gamma rays were the first carcinogenic agent used in the laboratory to produce experimental cancer in animals. Review of the literature shows that almost any tissue of the body can become malignant under favorable conditions of exposure. In most instances, these exposure conditions in-

volve repeated or chronic irradiation of a relatively small amount of tissue with large doses of radiation totaling several thousand roentgens.

This is not the kind of radiation carcinogenesis I shall consider today. Instead I shall discuss malignancy, particularly leukemia, in human populations in which the total body of each individual, or a substantial portion of the body, has been exposed to ionizing radiation. Only five such populations have been studied to date.

The first group is composed of radiologists. The incidence of leukemia and the life span of American radiologists has been the subject of a number of studies since 1942. It is well established, I think, that the incidence of leukemia in American radiologists is higher than that in males of the same age in the general population, or in other medical specialties. It has been shown recently that the life span of this group is not shortened and, except for skin cancers, particularly in the early workers in the field, the incidence of cancer it not increased over that in the general population. On the other hand, since 1921 the incidence of leukemia in British radiologists is not higher than might be expected. This has been attributed to better safety precautions used in Great Britain.

Although much has been made of the increased number of cases of leukemia in radiologists, the number of people actually involved is small. There have been thousands of workers in this field since 1900, yet in the literature up to 1948 I was able to find only 37 published cases of leukemia in x-ray workers.

The second exposed population consists of the Japanese who were in Hiroshima and Nagasaki at the time of nuclear detonations in 1945. The leukemia rate in these groups varied with the distance of the individuals from the hypocenter underneath the explosion. The dosage received by these populations is uncertain, but it seems clear that in the higher dose range the leukemia rate increases as the dose increases.

The third population is composed of patients with ankylosing spondylitis treated by x-rays and recently studied by Drs. Court Brown and Doll under the auspices of the British Medical Research Council. In a group of about 13,000 patients they found 32 definite cases of leukemia and 5 probable cases. In these patients the incidence of leukemia was clearly proportional to the dose, when more than 500 roentgens were absorbed in the spinal bone marrow.

The fourth population comprises children treated in infancy for

alleged enlargement of the thymus gland. Dr. Lenore Simpson and I have reported a series of 1700 children so treated between 1925 and 1950. A follow-up of about 90 per cent of these children showed that the number of cases of leukemia is approximately ten times the expected number in a group of children of this size and of this age distribution, and the number of cases of thyroid cancer is almost 100 times that expected.

The fifth and last population group is composed of children exposed to radiation in utero when their mothers were given radiographic examinations during pregnancy. The survey of these children was reported recently in the *British Medical Journal* by Dr. Alice Stewart and her colleagues. This is the only retrospective study of the five I have just mentioned. It shows that the mothers of children dying of leukemia or other forms of cancer before the age of 10 give a history of more frequent x-ray examination during pregnancy than do the mothers of matched control children. The percentage difference in the two groups is small—approximately 7 per cent of the mothers of the control children had this type of examination and 14 per cent of the mothers of the children with cancer or leukemia were examined in this way. Thus there is an excess of from 4 to 7 per cent of prenatal exposure in the leukemia and cancer group.

I cannot discuss these studies in detail but I would like to mention two questions which they raise.

The first: is there a threshold dose which must be exceeded before radiation can induce leukemia in man? I think no one can doubt the association between prior radiation exposure and leukemia as indicated by the studies just mentioned. Also, it seems clear from the studies on the Japanese and on the British patients with ankylosing spondylitis that there is a relationship between the incidence of leukemia and the dose in the higher dose range. One cannot be certain, however, that such a relationship exists in the low dose range. I don't think we can answer the question, whether or not radiation leukemogenesis is a threshold reaction, with the information we now have at hand. But we can reconsider the studies on the Japanese and on the patients with spondylitis, both of which furnish enough cases for us to at least attempt to relate the dose and the leukemia incidence. Also, I don't think we can depend too much upon the Japanese data in the low dose range, since the dosage data are not precise and there are uncertainty factors, such

as shielding, about which we know nothing. In the current United Nations report Dr. Neil Wald has pointed out that those Japanese who received an estimated average dose of two rem have a *lower* than normal incidence of leukemia.

Using the data of Court Brown and Doll, the curve of leukemia incidence in their patients with spondylitis, plotted against radiation dose, can be extrapolated back into the low dose range. Here it is seen that the dose associated with a doubling of the spontaneous leukemia rate is of the order 100 r to the spinal bone marrow. This would suggest that radiation leukemogenesis is a non-threshold response. But I don't think their data are entirely convincing, for three reasons: first, the number of cases receiving less than 500 r is small, only 3 of their 37 patients, so that one cannot be sure where to draw the curve in this region. Secondly, the incidence of leukemia in untreated patients with rheumatic diseases of various sorts seems to be higher than it is in the general population. This is the subject of an as yet unpublished report by Drs. Abbatt and Lea of the British Medical Council. Thirdly, the same sort of non-threshold response described by Court Brown and Doll for spinal marrow dose is not found if dosage is plotted in another way, that is, in terms of the integral or volume dose.

Also of great interest, in connection with whether radiation leukemogenesis is a threshold response, is the analysis of E. V. Lewis published in 1957 in *Science*. He considered all the irradiated populations, which I have mentioned, except for the children exposed prenatally. Using certain assumptions as to doses, he came to the surprising conclusion that in each population the probability of developing leukemia per roentgen per year is approximately the same. That is 1 to 2 x 10^{-6}.

The implication of this study is that each roentgen is equally effective in producing leukemia, no matter how large the amount of tissue exposed and no matter whether the exposure is acute or protracted over a long period of time. If true, this suggests that radiation leukemogenesis is a non-threshold reaction but, as I pointed out, with the evidence at hand, I don't think we can draw any definite conclusions at this time and we must keep an open mind.

The second question I would like to pose is this: Can irradiation of the entire body, or of a large portion of the body, cause cancer other than leukemia? In the data that is available from studies in *adult* populations I think we can safely say that there is no evidence, at this time,

that an increased cancer rate occurs in populations receiving only total body or almost total body exposure. This does not seem to be the case in children, and I would like to mention briefly the study that Dr. Simpson and I have made in children who were irradiated in infancy for alleged enlargement of the thymus gland.

Dr. Simpson has recently added 700 children to our original series of 1700, bringing the total up to 2400 children treated between 1925 and 1950.

(Slide) The first slide shows the number of cancer cases actually observed in this group of about 2400 treated children and the number expected. We expected to find 3.6 cancers in a group of children of this size and with this age distribution. We found 21 cancers. Cases of thyroid cancer expected were .06, eight were found; 0.9 cases of leukemia were expected, actually nine were found. We used as controls the untreated siblings of these treated children. The number of children involved was roughly the same in the two groups, and 4.3 cases of cancer were expected in the untreated siblings. We found six cases of cancer. There were no cases of thyroid cancer or of leukemia in the control group.

(Slide) This shows essentially the same data as appeared on the first slide. The cases have been broken down according to the method of treatment, and I would like only to point out group C, in which the incidence of malignant disease is especially high. Of 268 children treated and followed for an average of 14 years, there were two cases of leukemia, six of thyroid cancer, and three of other forms of cancer. This means that about 4 per cent of the children so treated eventually developed a cancer of some type. I should also point out that in this treatment group the doses used were high, the treatment fields were large and the treatments were repeated several times.

(Slide) In this slide we have broken down our cases according to the total dosage given to the child. Let us combine the first two columns, in which the children received less than 200 roentgens, and the second two, in which the children received 200 or more roentgens. Four of the nine cases of leukemia occurred in 1075 children receiving less than 200 r, and five cases occurred in approximately the same number of children receiving more than 200 r. In leukemia in children, therefore, we could find no correlation between dose and incidence of leukemia. Of all the other forms of neoplasia mentioned here, only two occurred in the group

of children receiving less than 200 r, one a thyroid adenoma and the second an osteochondroma. All the others occurred in children who were given more than 200 r. In the other forms of cancer there does seem to be some relationship between dose and cancer incidence.

In closing, I should point out that this last study in the children just mentioned is not conclusive since the control group for comparison with the treated children is not ideal. We cannot say with certainty that the children diagnosed as having thymic enlargement are not predisposed to develop cancer or leukemia, even though they had no x-ray treatment. This seems unlikely to me, and in support of this belief I can cite a current study we are doing on children given x-ray treatment for other conditions, in which two cases of leukemia were found in a group of approximately 75 children treated for pertussis in the 1930's.

MODERATOR RALL: These are somewhat disturbing findings, but we have another reason for concern about radiation. Geneticists have been telling us for some time about genetic damage produced by irradiation; how this may result from extremely small doses, is generally damaging, and is always significant. I think it was Dr. Mueller who said that the most precious heritage we can give our children is an untainted germ plasm. *Now Professor Dobzhansky will tell us something of the relationship between genetics and radiation.*

PROFESSOR TH. DOBZHANSKY: Much remains to be learned about the effects of high-energy radiations on living matter. At the present level of knowledge the fundamental distinction appears to be between the effects on the individual exposed and the effect upon his progeny. The former are referred to as physiological and the latter as genetic damage. Yet there may exist an intermediate zone if, for example, it will be demonstrated that certain malignant conditions, such as leukemia, are due to changes in the genetic apparatus of irradiated cells.

Concerning the problem of genetic damage, with which I happen to be more familiar, its fundamental characteristic is the absence of any threshold of radiation exposure below which genetic changes do not occur. The basic genetic radiation damage, in contrast to the physiological damage, is simply proportional to the amount of exposure. An exposure incurred within minutes or seconds from an intense burst of radiation causes the same damage as is produced by accumulation of small doses over years or decades. As far as the genetic radiation effects are concerned, there is no such thing as a safe or permissible amount.

Beyond these simple facts begins a zone of uncertainties. We do not have adequate data concerning the proportion of the mutational changes in man, or for that matter in any other organism, which can be ascribed to the naturally occurring radiations and which are induced by causes other than radiation. Consequently, the estimates of the so-called doubling dose are at best tentative. There may be no such thing as a fixed doubling dose for all mutations. The most serious gap in our knowledge is, however, due to the fact that almost all the research so far has been directed towards finding out how many mutants radiation induces, while the no less important problem of the fate of the mutants in living populations has been neglected. This field may be fraught with surprises. Indeed, if most mutations are harmful and recessive, the over-all genetic damage would be close to the sum of the mutation rates. If most of them are harmful and even slightly dominant, the genetic damage would be close to double the aggregate mutation rates. However, the mutations which are harmful when homozygous, but enhance the Darwinian fitness of heterozygotes, are a separate class. Their fate in sexual populations is governed chiefly by natural selection, rather than by the rates of their origin by mutation. What the relative frequencies of these types of mutational changes are is a matter for future investigations. Before we learn more about this matter, all the numerical estimates of the genetic damage in human and other populations give a spurious appearance of exactitude to actually very shaky knowledge.

MODERATOR RALL: We shall undoubtedly return in the question period to problems in the intermediate zone of uncertainty, because it is about this zone that we most desire information. *Finally, Dr. Russell Morgan will discuss the concept of the maximum permissible dose.*

DR. RUSSELL H. MORGAN: As Dr. Rall has just said, I should like to speak for a few moments on the maximal permissible dose as a concept. I do so in the hope it may stimulate your thinking, because it is an important part of the radiation hazard picture, as developments over the next few years will unfold.

The maximum permissible dose, as you know, is generally defined as the quantity of radiation to which an individual may be exposed, below which one may expect no significant biological harm, and above which there is sufficient indication that harm will result. And one will hope that the maximum permissible dose will not be exceeded.

This concept developed in the early days of radiology, when

radiologists were first beginning to appreciate the significance of the effects of ionization. Certain stipulations were formulated at an early date by the National Committee of Radiation Protection as to what the maximum permissible dose should be for individuals working with radiation and for individuals in the population at large, as determined from early radiobiological data regarding radiologists. Other speakers this afternoon have made it clear that radiological data at the present time are, at best, rather meager, that is, data relating biological effect to radiation dosage. In the 1920's when the maximum permissible dose concept was first developed, it was even more meager. This concept was developed, in spite of the meager radiobiological information then available, on the assumption that radiation, as a harmful agent, might have characteristics similar to other toxic agents. Many of these other agents behave in such well-defined ways that maximum permissible doses are easily determined. For example, if you plot the biological effect of almost any hazardous toxic agent against the dose, you will find that the resulting curve has certain well-defined characteristics. The curve is essentially one with a sigmoid type of distribution. Most toxic agents have one other characteristic, to be observed when it is possible to maintain the dose below a certain critical level, when the individual who receives the dose will, in time, recover and not suffer any long-lasting ill effects. In short, most toxic agents have a threshold below which complete regression of the toxic state may be expected and show no undesirable biological effects after the toxic agent has been removed.

This raises a question in this sixth decade of the 20th century as to whether radiation behaves as these conventional toxic agents do. When radiation is applied in huge doses over a short period as received by the population of Hiroshima during the bombing in World War II, the effects of the radiation received were very similar to that of the curve previously shown. Should one measure the biological effect in terms of lethality, placing a percentage scale on the ordinate side of the graph and plotting on the abscissa the dose received by the population, one would find that a typical sigmoid distribution had been obtained. Furthermore, in most instances, if the dose were below 100 roentgens of whole body radiation, the individual usually recovered. By and large, the individuals in this group recovered rather completely, showing no lasting bone marrow changes of the type which killed those who received very much higher doses during the severe radiation exposure.

It has already been mentioned that the acute radiation syndrome does not occur with the low dose situation. Although the evidence is not conclusive, it would appear that if the biological effect is plotted against radiation dosage, instead of getting a sigmoid type of distribution, the result would show more of a straight line distribution.

Furthermore, it has been repeatedly noted that no threshold effect appears, that nowhere is there a point where one can predict that no radiobiological effect will occur. Indeed, one may expect radiation effects of one sort or another, genetic, leukemogenic, life-shortening, to progress gradually from the point of dose zero and to become increasingly severe as the dose increases. I think it is rather clear that radiation at the low dose levels—and it is these levels with which most of us are concerned—does not behave like the ordinary toxic agent.

Therefore, since radiation does not behave as do ordinary toxic agents, many of us believe that the maximum permissible dose, based upon the concept that radiation is the same as any other toxic agent, is probably an unsound concept on which to base future work. In its place a much sounder notion is that in which radiation should be regarded as being an agent presenting a progressively increasing hazard as the dose increases. Radiation cannot be considered in terms of white or black, as the maximal permissible dose concept implies, but should be regarded as a graded series of risks starting from the zero dose level.

For example, let us consider the radio-strontium levels in milk which have been discussed so much in the past and which will, I am sure, be discussed far into the future. The National Committee on Radiation Protection has currently set a maximum permissible level of 80 micro-microcuries per liter for radio-strontium in milk. Does this imply that, should the strontium levels in milk exceed 80 micro-microcuries per liter, the public health authorities should immediately go out and condemn all the milk, kill all the cattle and take out of service all the farmland where such milk is produced? Were the scientific evidence for biological effect versus dosage unquestionably sound, there might be some justification for taking so drastic a step. But, as you have heard here this afternoon, the scientific evidence is not complete. A great deal of scientific evidence will be produced in the future. Whether this 80 micro-microcurie level is too low or whether it is too high is not now known. One thing that is known to us is that radiation hazard increases progressively from dose zero, and therefore it seems wise not to con-

sider the problem in hard and fast terms, black or white, but as one in which the radiation hazard increases progressively. And we must learn to set up standards of control to meet these biological facts.

MODERATOR RALL: I have a question which takes us away from cancer for the moment: with regard to children, and in expectant mothers in the fourth or fifth months of pregnancy, where radiation has an influence upon the normal growth and development of the skeleton of the fetus, *would diagnostic radiation at that time have an effect on the fetus or child sufficient to cause cerebral damage and metabolic changes?* Dr. Morgan, would you attempt to answer this question as I interpret it: *will prenatal diagnostic irradiation have immediate, long-term, or insidious effects?*

DR. MORGAN: It is not easy to answer the several questions which you raise—not easy because of the complexity of the available radiobiological data. However, I think that one can say this, that prenatal radiation produces a number of long-term effects—genetic effects—and the effects which Stewart has mentioned in leukemogenesis of children irradiated in utero. The amount of radiation necessary to produce acute change, acute symptoms, is so large that I think it is most unlikely that such circumstances will exist in the case of any pregnant mother, except under the horrible conditions of atomic warfare, when there would be no control. Where there is control, the amount of radiation used will not be sufficient to produce acute manifestations.

MODERATOR RALL: *Do you have anything to add to that, Dr. Hempelmann?*

DR. HEMPELMANN: It is true that animal experimentations have shown the developing embryo to be very sensitive to the action of radiation, and it has been demonstrated that certain developmental abnormalities occur after exposure to quite small doses of radiation, especially in the very early phases of pregnancy. Dr. Liane Russell of Oak Ridge finds that she can observe changes in mice after single doses as small as 25 r.

MODERATOR RALL: How would you interpret the observation that the leukemogenic doses in the Court Brown study were of the order of several thousand r, at least to some tissues? The doses that you studied were of the order of some hundreds r and the doses that Stewart noted in fetal life were of the order of 10 r. Perhaps these are inversely correlated with the age of the individual that had received them. In short, *do you think children or fetuses are more susceptible to carcino-*

genic effects of radiation than adults, or do you think this is a statistical quirk?

DR. HEMPELMANN: When one looks at the gross data, it would certainly seem to be true that the younger the individual the greater the sensitivity to the carcinogenic action, at least leukemogenic action, of irradiation, and this I hoped to be able to prove at this meeting. When I tried to repeat E. B. Lewis' calculations with the two populations which I knew best, and in which I thought the radiation exposure data were accurate, that is, Court Brown's patients with spondylitis and our children, I arrived at essentially the same answer. I could not find any great difference of probability of developing leukemia per r per year using his concept, even though all our children were treated with much lower doses than were the patients with ankylosing spondylitis. I am afraid I just cannot give you a good answer. I thought I would be able to, but now I am confused myself.

MODERATOR RALL: Dr. Dobzhansky, here is a question addressed to you. *Is it conceivable that genetic effects may not be directly related to dose, if certain time-dose exposures produce death of the germ cell while other time-dose exposures do not? Can this play a role?*

DR. DOBZHANSKY: Thus, far, to my knowledge, the existing data agree best with the assumption that such proportionality does exist. There are, of course, data collected by experiments on animals, chiefly lower animals, Drosophila. As long as there is no serious ground for supposing otherwise, I think by far the most reasonable assumption to be made is that this simple direct proportionality does exist. That is true for both mutant and non-mutant.

MODERATOR RALL: *On a priori grounds, if mutations are caused by some disturbance in deoxyribonucleic acid metabolism or the structure of the double DNA molecule, it seems inconceivable that any dose of radiation—if this is an ionizing event that occurs in the vicinity of this complex structure and damages it—that such damage would not cause mutation? Is that not so?*

DR. DOBZHANSKY: That presupposes something like the so-called "target theory" of the production of mutation which is, of course, not the only possible one and it is, in fact, one which many people have doubted. So I personally would prefer to stand simply on empirical grounds and say the existing information seems in complete agreement with this supposition. It is about as simple as that.

MODERATOR RALL: This question is addressed to Dr. Morgan. *Is there definite or sound evidence that the cumulative effect of radiation is less if the exposure occurs at infrequent intervals?* This isn't specified, so you can, perhaps, specify it if you care to.

DR. MORGAN: I think that this question indicates that a moment or two should be taken to clarify what is meant by cumulative effects which are not lasting.

As far as the cumulative effects are concerned, in general this relates specifically to the genetic effects, to the leukemogenic effects and to the aging effects of radiation,—the long-term effects, when it does not make much difference whether you deliver one roentgen per day for ten days or ten roentgens every ten days. I am using rather large doses as an example, but these numbers are still appropriate.

The changes of recovery are found when the dose is an acute one—the dose of the sort that those in Nagasaki and Hiroshima received, 200, 300, 500 or more roentgens, to their entire bodies. Here, in addition to the genetic effects and in addition to whatever factors may be responsible for the production of leukemia later on, there is enough disturbance of the biological mechanism of the bodies of the survivors of those explosions to produce, in addition to the long-term effects, very severe short-term biological effects which were brought under control as soon as the severe immediate results of the radiation passed away and the individual returned to "normal".

The extent of these acute changes is directly related to the rate at which the dose is given. If a dose of 1,000 roentgens, instead of being given in a single dose as in the bombings of Japan, were given intermittently to individuals in 100 roentgen increments at monthly intervals for 10 months, the acute effects, including bone-marrow depression, from which there may be recovery, would not be so severe as would result from the single massive dose, and the great majority of the individuals exposed to the multiple smaller doses would recover.

Therefore it is important in evaluating radiological effects to classify them as long-term effects and short-term effects, remembering that the short-term effects are those from which recovery may occur.

MODERATOR RALL: There are, then, these two factors: the proportion of damage that is irreparable, and the rate of recovery of the reparable fraction. There have been many attempts to estimate these in the human and it seems to me the idea has come to be accepted, that only 10 or 20

per cent of the damage from any large dose of radiation in an acute situation is irreparable or non-recoverable and the recoverable part will progress at the rate of five per cent per day. Are there any other comments to make on these numbers? They are important numbers. We would certainly like to know their precise value.

DR. MORGAN: I too think they are important numbers. I would not want to comment on them because I don't think they are supported by enough good data to make them significant.

MODERATOR RALL: *Or any data?*

DR. MORGAN: There are some data.

MODERATOR RALL: *One has to extrapolate?*

DR. MORGAN: Sufficient data. All data have some merit, I suppose.

MODERATOR RALL: *Dr. Laughlin, you have been asked to repeat the comparative bone marrow dose from a diagnostic chest x-ray, the 14 x 17 ordinary chest x-ray, versus the photofluororoentgenogram. I think someone was impressed by the difference in the figures you showed.*

DR. LAUGHLIN: This does not necessarily apply to all installations, but in many instances the photographic unit has been shown to require more radiation, possibly ten times as much. In a case where the bone marrow dose for a *photographic* chest film would require possibly 100 milli-r average dose in the active bone marrow, the corresponding figure for the *ordinary* 14 x 17 film would be about 10 or 15 milli-r.

MODERATOR RALL: Here is a question that I think anyone might be interested in answering: *The only good human clinical experiment relating radiation to mutation is Ira Kaplan's, in which he delivered 225 r to the gonads of several hundred women. With some 600 progeny down to the second generation, there have been no major mutations and no more than the normal number of minor mutations. What do you conclude from this?*

DR. DOBZHANSKY: I regret to say I am not familiar with the experiment in question.

MODERATOR RALL: I think the experiment consisted of the radiation of women who were referred for treatment of fertility problems. Their ovaries were radiated to the extent of several hundred r and their children and their grandchildren were studied. *Do you have any comment on the mutations, whether you would expect to see any obvious monsters or not, or what would you expect to see?*

DR. DOBZHANSKY: Obviously, as a matter of statistics, I prefer to say

nothing about this without being familiar with the experiment in question. I rather wonder whether the material investigated has been sufficient in numbers to be statistically significant.

MODERATOR RALL: We shall put it this way: *Would one expect to find the fraction of mutations which are recessive so large that one would not expect to see them expressed in this population until they were present in the homozygous state?*

DR. DOBZHANSKY: Oh, yes, certainly. What radiation does is to add to, super-add if you wish, a certain number of mutants on top of the existing mode of mutations. If one were able to investigate a statistically sufficient sample in the progeny of irradiated persons, a certain number of dominant mutants would presumably be detected.

MODERATOR RALL: *What number?*

DR. DOBZHANSKY: That again would be decided. It is a little foolhardy to say.

MODERATOR RALL: *One per cent?*

DR. DOBZHANSKY: In a sufficient number of individuals one would expect to see some dominant mutants. Recessive mutants of course would not be seen in the immediate progeny. I repeat I am not familiar with that.

DR. MORGAN: How many patients were irradiated in Dr. Kaplan's series?

MODERATOR RALL: As I recall the paper, it reported on several hundred women who were irradiated and perhaps 500 or 600 children and grandchildren were studied.

DR. MORGAN: And the dose to the average female parent was something of the order of 200 roentgens?

MODERATOR RALL: Yes.

DR. MORGAN: Let us say there were 500 mothers. We shall speak in round numbers but quite obviously the changes that one may expect to receive from the delivery of 200 r to 500 mothers is no more than the delivery of 1 roentgen to 100,000 mothers and, in this sort of experiment, we are not likely to see large amounts of genetic damage in one or two generations, bearing in mind that most of the mutations will be recessive.

The experiment is one which appears impressive on first glance but which, from a statistical viewpoint, has many shortcomings.

MODERATOR RALL: *The main trouble appears to be that one would*

expect to have almost all the mutations recessive and expect to see very little effect from these unless one could determine the patients' life expectancy and compare that with a control group?

DR. MORGAN: Yes.

MODERATOR RALL: *None of these have anything to do with whether there were any obvious mutations?*

DR. MORGAN: I don't think the audience should go away with the impression that, just because this experiment does not give conclusive evidence, the radiobiological data on this general subject constitute one complete hiatus. Quite the contrary. The evidence which is at hand indicates that if a population such as that of the United States were exposed to certain amounts of ionizing radiation to their gonads, one could anticipate that undesirable consequences of a very important nature would occur over a number of generations.

MODERATOR RALL: Here is a practical question that concerns most physicians: *Is the panel opposed to some relatively common but perhaps non-essential radiation exposures, such as routine gastrointestinal series, dermatologic treatment or therapeutic irradiation for inflammatory conditions such as bursitis or tendonitis? Professor Morgan, that is up your alley!*

DR. MORGAN: Forgive me for apparently monopolizing this microphone. I think one can say with great certainty that any unnecessary radiation should be avoided. There is no question about this. The big difficulty consists in establishing a definition of what is unnecessary and what is necessary. Were I an individual who had a duodenal ulcer that was giving me a great deal of discomfort, I would, more than likely, want a gastrointestinal series. Some gastrointestinal series are conducted on people whose pathology is undetermined. They have a series for diagnostic purposes. Here the balance between the radiobiological hazard and potential benefit is rather inconclusive. I find it extremely difficut to decide whether such radiation is necessary or not. When people ask me these questions in such situations, I usually sit down with them, present the available data and point out what their chances are of developing leukemia on the basis of known facts, what the chances are that their life expectancy may be shortened by a day or two and then let them decide.

When these examinations are to be done by careful people, where the radiation dosages are low, the numbers usually produce values which

make it seem desirable to go ahead with the procedures. On the other hand, if the examinations are to be made under conditions where the dose may be large, this should cause the individual to pause for thought. I don't think one can go any further at this time; the currently available data are not reliable enough to warrant saying more.

MODERATOR RALL: Sometimes you have to. *Are you for or against the mass chest survey programs, the photofluororoentgen mobile chest units?*

DR. MORGAN: For cancer of the lung?

MODERATOR RALL: *Cancer and tuberculosis.*

DR. MORGAN: For cancer of the lung I think the evidence is definitely against these programs, on several grounds. First, the number of cases that may be picked up is not greatly different from the number of potential cases of leukemia which may be produced by the radiation. Also, until the surgical and radiation therapy statistics on cancer of the lung, at any stage, become much better than they are now, there is much question as to the wisdom of studies of this sort. A few years ago we undertook a study in the field of gastric cancer. We x-rayed more than 10,000 individuals over the age of 40, in an effort to pick up unsuspected lesions. We learned that the photofluorographic techniques were quite adequate to pick up early cancer. We found unsuspected cancers in only between one in 500 and one in 1,000 of the patients admitted to our hospital. On the other hand, in picking up these cases the amount of time spent, in terms of professional time and effort, was enormous, and it became a tedious and depressing activity for the physician to read these films. This is just one more reason why such mass surveys are of limited value.

In answer to the question about cancer of the lung, I would say that these mass surveys are almost doomed to failure at the outset, not only from the radiation hazards standpoint but, perhaps more important, because of a number of professional factors.

MODERATOR RALL: Formerly there was a policy at the National Institutes of Health to get a photofluororoentgenogram of each patient on admission. We abandoned that and now plan to get a regular chest x-ray film only if there is some definite indication for it.

Here is a question, perhaps the last one: *What can physicians and radiologists do to decrease the radiation hazards? Can we increase protection, Dr. Laughlin?*

DR. LAUGHLIN: I think there are a number of things which may be done and which are recommended by the American College of Radiology, on which Dr. Morgan can speak much more fully than I. The control of the field size so only the pertinent area is in the radiated field, the use of proper filtration so that the more effective portion of the spectrum of x-rays is employed, are just two of the many things that can be used. I think Dr. Morgan can add to this list.

DR. MORGAN: The limitation of field size during fluoroscopy is certainly one of the things which is of greatest use in reducing radiation exposure. I happened to grow up in an environment where the fluoroscopes used did not have a field larger than 4 by 7 inches. Many of you who are fluoroscopists will be shocked at this and indeed I was, when my chief argued that this area was enough for diagnostic purposes. Since that time I have become convinced that it is large enough, although it takes a little training and experience to get used to small field sizes. Nevertheless, this is a good technique for reducing radiation exposure.

Incidentally, there has been some talk about some other things, the gonadal shield and the like. One point about radiation which I think might be worth discussing for just a moment is that the gonadal dose, which an individual may receive during diagnostic x-ray procedures, is usually received not from radiation coming to the gonads directly from the x-ray tube (unless the gonads are in the direct line of the beam), but instead, comes from radiation which leaves the x-ray tube, hits the tissues under irradiation and then scatters to the gonads. As a result, a gonadal shield, a shield of lead, placed over the testes, or placed on the abdominal wall in the case of a female patient, is essentially useless in reducing gonadal exposures, for the simple reason that, in the case of a chest exposure, the radiation comes from the x-ray tube, falls on the chest, and then scatters directly down the long axis of the body to the gonads, undercutting the superficial shield rather effectively. Of course in a male, one could have gonadal protection in which the testicular tissues are completely enclosed. This would be quite effective. So far, however, none of these, practical for every day use, has been developed.

MODERATOR RALL: We have exceeded our allotted time. I wish to thank the panel members for participating in this discussion.

STUDIES IN MYASTHENIA GRAVIS: TECHNICAL CARE OF THE THYMECTOMY PATIENT*

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ALTHOUGH the relationship of structural alteration of the thymus gland and myasthenia gravis is still not established[1, 2], surgical extirpation of this gland as a therapeutic measure continues to undergo evaluation in selected cases[1, 3]. In a myasthenic patient this, or any type of major surgery, carries specific implications and risks different from those in any other group of patients. The selection of myasthenic patients for thymectomy has been the subject of many papers[1] and will not be dealt with in detail here. It is important to mention that recent experience indicates that thymomas associated with clinical myasthenia are malignant in an extremely high proportion of cases[2]. This evidence dictates thymectomy in these patients, without consideration of other factors.

Successful preoperative preparation, performance of surgery and postoperative care of the thymectomy patient are the results of team effort comparable in scope to techniques used in open heart surgery. This paper describes methods and procedures evolved at The Mount Sinai Hospital, New York City, for the technical care of the patient undergoing such surgery. These procedures have resulted in a safe, smooth, effective performance of a major surgical maneuver in an extremely brittle group of subjects.

Different phases of the total management will be described so that the contribution and roles of all personnel and equipment may be indicated. This experience covers a series of 14 thymectomies performed in the past year, of which six were thymomas.

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Preoperative Phase

Because of the nature of this disease, the myasthenic is emotionally involved more than most patients with chronic illness. Evaluation of drug dosage is partially absolute, but when a state of stress or trauma supervenes, the intelligent and conscious cooperation of the patient with his physicians is of utmost importance. Therefore every effort is made before operation to acquaint our patients with all of the discomforts, apparatus and surroundings they will encounter. This includes meeting with patients recently thymectomized, visits to the recovery room and interviews with the staff involved. The medical staff becomes acquainted with the patient and attempts to evaluate his or her ability to cooperate. All questions are answered, within the limits of the individual's capability of assessing such information. The patient is shown how to cough and breathe and is familiarized with the mechanical respiration equipment that he may require.

A preoperative medical profile is obtained with particular emphasis on multiple points.

1. Laboratory Data:
   - Chest x-ray including tomography
   - Electrocardiogram
   - Determination of vital capacity
   - Blood chemistries including carbon dioxide, blood urea nitrogen, and a complete coagulation study
   - General medical status
2. Selection of proper time for surgery:
   - Emotional preparedness
   - Post menstrual phase for premenopausal females.
   - Freedom from even the most minor respiratory infection, as a compromised respiratory tree is the commonest cause for postoperative difficulty. Operation is postponed if there is evidence of such infection.
3. Preoperative x-ray therapy:
   - Extensive experience with such therapy has been gathered by Keynes[4]. Ease of the subsequent surgery, with shrinkage of the thymus or thymoma, is reported. At times, we have encountered serious difficulties after radiotherapy, as follows:
     a) Development of variability of response to cholinergic drug therapy, with a narrowing, and even inversion, of the therapeutic index[1].
     b) Complete unresponsiveness to cholingeric drugs with development of myasthenic crisis.

c) Radiation pneumonitis.

d) Surgical technique may not be facilitated by preradiation because of the residual increased vascularity of mediastinal structures.

e) Histologic evidence suggests that only the thymocytic (lymphocytic) element of the thymus is sensitive to x-ray exposure. These cells appear to have neither malignant nor "myasthenic" potential, which properties are related to the thymic epithelial cell. The latter is highly radio-resistant, even to supervoltage therapy[1, 2].

4. Preoperative adjustment of drug therapy:

No attempt is made to treat the patient with parenteral therapy until the morning of surgery. For several days prior to operation, cholinergic drug control is maintained only at levels compatible with comfort, with no effort made to achieve scrupulously optimal levels of muscular strength. Oral dosages thus arrived at are translated into the equivalent parenteral dosage[1] which is administered at a time calculated to be effective through the period of anesthesia induction. No supplementary cholinergic medication is given during surgery.

Technique of Anesthesia

Premedication consists of either meperidine (Demerol) alone or in combination with promethazine hydrochloride (Phenergan), given intramuscularly one hour before surgery. Atropine and scopolamine are avoided because of the thick secretions that follow their use and because these agents may mask overdose of cholinergic medication.

The neuromuscular and pulmonic aspects of the problem influence directly the choice of anesthetic agents and techniques. The nature of the procedure requires complete control of respiration. The anesthetic agent used must be capable of producing any level of anesthesia necessary, must be quickly eliminated, must provide for the inclusion of a high level of oxygenation, and should not require routine supplementation with muscle relaxants. The anesthetic of choice should not promote secretions or produce postoperative depression of the patient. The agent that most readily meets these criteria is cyclopropane. Following transtracheal cocainization with 2 ml. of 5 per cent cocaine, the patient is given a small dose of thiopental sodium intravenously. As soon as there is loss of consciousness, intubation is performed. Following the transtracheal cocainization, this procedure can usually be done without the use of muscle relaxants. Anesthesia is then continued with cyclopropane and oxygen. With proper assistance, controlled respiration is established

without difficulty. Only minimal amounts of cyclopropane are required. In the few patients in whom a muscle relaxant is necessary, the agent of choice is succinylcholine. All relaxants in the non-depolarizing group are absolutely contraindicated (curare as d-tubocurarine, gallamine and mytolon)[5]. Control of ventilation may be accomplished manually by means of a mechanical device, depending upon the preference of the anesthetist. Inasmuch as copious amounts of secretions may be produced suddenly, frequent tracheobronchial aspirations are necessary, and this may prove to be the most difficult part of the anesthesia.

A very light plane of anesthesia is needed, with adequate ventilatory exchange being the important feature so that there is no retention of carbon dioxide or bronchial secretions.

Rarely, a patient may be encountered who, in addition to myasthenia, suffers from bronchial asthma. In this case the use of succinylcholine and nitrous oxide oxygen is safer than cyclopropane. If bronchospasm develops in such a subject, supplements of succinylcholine, helium and aminophylline are all of value. Because of its tendency to create a curariform type of neuromuscular block, as well as being capable of increasing bronchial secretions, ether is contraindicated for use as the anesthetic agent[6].

The tracheobronchial tree must be completely cleared before the patient leaves the operating room. Simple auscultation of the chest will help to determine this. A chest x-ray is done routinely upon arrival in the recovery room. If there is any question of adequacy of lung expansion, or should pneumothorax or atelectasis be suspected, the x-ray is taken before the patient is moved from the operating table.

It is most desirable that the patient be awake and have an active cough reflex before leaving the operating room.

Surgical Technique

A sternal splitting incision, carried in the skin from the jugular notch to the fourth intercostal space, is employed. The sternum is split longitudinally with due regard for the length of the incision and then is severed laterally into the interspace. Upon insertion of a self-retaining retractor, excellent exposure of the thymus is obtained over its entire length and breadth. Such exposure, as well as the good chest wall stability afforded during the postoperative phase, makes this approach most satisfactory.

In patients without thymoma, the bilobed, delicately encapsulated thymus is readily evident, lying in the loose areolar tissue of the anterior mediastinum. The two lateral thymic lobes may extend from the lower poles of the thyroid superiorly to overlie the pericardium inferiorly. They border on the phrenic nerves and particularly the left innominate vein, which at times may be completely surrounded.

In non-tumescent cases the gland is almost always readily dissected free from its bed. The operative management of the tumescent gland represents a more complex technical problem. It should be pointed out that this tumor bears different criteria for malignancy than most neoplasms in that these criteria are gross rather than microscopic. In histologic section the characteristics of malignancy are notably absent in even the most blatantly invasive tumor. The malignancy of this neoplasm is indicated by capsular and local invasiveness as well as by separate pleural and percardial implants[2]. Such secondary deposits may be found in both pleural cavities; and further, because of their mediastinal location, may escape even the most careful preoperative x-ray evaluation. Therefore the following are recommended:

a) Obligatory total thymectomy, rather than thymomectomy, in cases where the tumor is localized to one lobe.
b) Removal *en bloc* of any contiguous adherent structures that may safely be sacrificed.

In view of these facts, surgical management of the thymoma patient varies from case to case, depending upon the extent of the tumor. In practice, following the initial sternal splitting incision, the mediastinal pleura is opened widely, bilaterally, so that relation of the phrenic nerves to the tumor and the presence of any implants may be gauged. The tumor and any contiguous structure are then removed *en bloc*, including pericardium, pleura, innominate vein or any other tissues involved. In all cases a special attempt is made to preserve the phrenic nerves so that later respiratory excursions be affected as little as possible. The difficulty of the resection will, of necessity, be dependent on the degree of invasion found. Following extirpation of these tissues, the residual mediastinal structures are dissected free and cleared of any remaining fatty or lymphatic tissue.

In all cases, transpleural mediastinal drainage is obtained by means of intercostal chest tubes under water-seal suction. If neither pleural space has been entered during resection, the mediastinal pleura is opened

widely on one side to allow this drainage. Should both pleural spaces have been entered, bilateral chest tubes are used. Mediastinal collections of fluid, serum or blood have been avoided by such tubes and no problem has been occasioned by their presence even when the use of a Drinker respirator was required. In general, chest tubes may be removed within 48 to 72 hours.

An obligatory tracheostomy is performed in the operating room at the close of the procedure, as soon as adequate spontaneous respirations have become established. In order to avoid communication with the upper part of the mediastinal dissection and to facilitate care in a respirator, the tracheal stoma is placed as high as possible, usually through the first or second cartilaginous ring. Tracheostomy is performed before extubation. The largest caliber tracheal tube accepted is employed with an inflatable rubber cuff affixed to its exterior. Such a cuff prevents, if necessary, any regurgitation of air through the oro- and nasopharynx if the myasthenic's weak glottic closure is unable to cope with the stress developed by mechanical positive pressure respiratory assistance. Cuffing also allows only a minimum of oropharyngeal secretions to descend into the trachea, removing a possible source of bronchial aspiration. The tracheostomy tube is doubly secured by skin sutures so that no future manipulation of the patient may dislodge the airway.

Postoperative Care

When the surgical procedures are concluded and the patient displays forceful spontaneous respirations, transfer to a "complete care unit" is effected. Intensive, continuous observation for several days is afforded the patient, within a locale containing all possible equipment required for any eventuality.

Surgical aspects of the postoperative care have presented few problems and follow the accepted principles employed in any type of thoracic procedure. Antibiotics, replacement of blood loss, attention to reexpansion of the lungs are scrupulously attended to. Fluid requirements are given parenterally for a somewhat longer period than usual, in view of the dysphagia so common in this group of subjects. Enemas are contraindicated since deaths have been reported following the use of this procedure[7].

The care of the tracheobronchial tree is of paramount importance. The profuse secretions often encountered demand frequent, exacting

tracheal and oropharyngeal suctioning. However, care must be taken to keep these secretions moist and fluid. Cold steam, with or without bronchodilators, is used. Atropine is employed only when the secretions are inordinately profuse. If, despite these measures, atelectasis or inspissation of secretions occurs, free and repeated use of bronchoscopy is employed. Bronchorrhea may persist for some time and care is taken not to remove the tracheostomy tube prematurely.

Maintenance of Adequate Respiratory Exchange; Management of the Myasthenic State

These two phases of postoperative management are closely related and require the closest cooperation of surgeon, internist and anesthesiologist.

In contrast to previously reported experience[7], little difficulty in maintaining respiration has been encountered in the immediate postsurgical period, since most patients display a marked, if transitory, improvement in their myasthenic symptoms. Therefore, no supplementation of the preoperative cholinergic medication has been given. Such management is continued for the first several days, in that cholinergic drugs are given only to maintain respiration, with no attempt to titrate to optimal muscular strength. The initiation of even this minimal drug therapy usually is necessary only after the first 18 to 24 hours. The use of drugs in this fashion has obviated cholinergic crisis and has minimized the hypersecretion inherent in the use of cholinergic drugs. All medication of this type is given on a demand schedule, confirmed by Tensilon testing and clinical response[8]. Demand for cholinergic medication has been found to vary widely from patient to patient and even by the same patient, with time. Postoperatively there is little relationship to the preoperative dose requirement, and, in general, no empiric statement of dosage is possible. The intravenous route of drug administration permits the best and safest control. The drug of choice is Mestinon bromide (pyridostigmine bromide). Not until oral feedings are tolerated can cholinergic drugs be given *per os*, because absorption from an empty gastrointestional tract is erratic and unreliable. This time coincides, in most patients, with a return of stability of the myasthenic state so that routine medication may be given.

The pain caused by the incision, chest tubes and bandages, when coupled with the muscular weakness of the patient, may not allow ade-

quate ventilation even with cholinergic medication. In such cases intermittent respiration assistance must be supplied. Occasionally this may be required at the conclusion of surgery. The Bird Residual Breather MK7 has proved eminently satisfactory. This device is a pressure-cycled ventilator which is either automatic or patient-triggered. If the patient fails to breathe within a predetermined interval, the machine can be adjusted to cycle automatically and inflate the lungs. A nebulizer is incorporated in the circuit. Adjustment is possible to control the amount of positive pressure, the duration of the inspiratory phase, the rate of ventilation and the degree of sensitivity of response to any attempt by the patient to initiate respiration. The length of the expiratory phase may also be preset and there is provision for manual control. This machine's great versatility, its ease of operation and the favorable comments of patients who had previous experience with other devices, have impressed us with its performance. However, in case of atelectasis or tracheal plugging, the Drinker respirator is superior in permitting better gas exchange, although not allowing the same nursing care or the same physical and psychological freedom for the patient. It is pertinent to mention that should intermittent positive pressure assistance be necessary, close attention must be paid to the total time during which the endotracheal cuff is inflated. If this time is too prolonged, necrosis of the tracheal wall may ensue. A far preferable course in such instances is the use of the Drinker respirator.

Narcotics (meperidine) and sedative drugs (promethazine hydrochloride and its derivatives, and phenobarbital) are used in minimal amounts. They need not and should not be withheld because of the myasthenic state.

A partial listing of general complications encountered and dealt with include: respiratory acidosis, carbon dioxide narcosis with delirium, hyperthermic states, loculated effusions and paroxysmal tachycardia. A specific complication is the peculiar addiction to respiratory assistance evidenced by some patients, even when they are demonstrably capable of good spontaneous ventilation. Because of this, only the briefest possible use of mechanical assistance is desirable.

Successful resolution of these and other postoperative complications has depended primarily upon the closest of observation and harmonious cooperation of the associated medical personnel, including superior nursing team care.

Continued convalescence takes place on a ward or private room basis after complete stabilization. Return to preoperative quarters has usually been possible on the fifth postoperative day.

Summary

Experience with 14 selected myasthenic patients undergoing thymectomy during the past year has led to the adoption of procedures which have been most satisfactory.

Cooperation of surgeon, anesthesiologist and internist, coupled with care of the patient in suitable surroundings, has permitted smooth performance of major surgery in a difficult situation. The contribution of each specialist is analyzed in terms of the particular problems presented by the myasthenic undergoing thoracic surgery. Discussion of total thymectomy is presented concerning preoperative, anesthetic, surgical and postoperative phases of management. Methods of choice are presented in each of these disciplines. The malignant potential of thymoma associated with myasthenia gravis makes surgery mandatory in these patients.

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REPORT ON ADOPTIONS*

BY THE

COMMITTEE ON PUBLIC HEALTH**

OF

THE NEW YORK ACADEMY OF MEDICINE

The Committee on Public Health became interested in the matter of child adoption in 1945, when as a result of the war and an increase in illegitimate births, a "black market" in infants developed on a national scale. Because of the threat to child welfare implicit in this process outside the law, five leading child placement agencies in New York City requested the Committee's assistance in formulating methods to correct the situation in the city.

The agencies submitted to the Committee for its opinion a number of amendments to the state penal law, the domestic relations law and the social welfare law, designed to make irregular adoptions difficult. At that time the Committee approved the intent of the proposed changes, but warned that legislation would not be effective until sufficient facilities could be set up to care for unmarried mothers. It was also recommended that an attempt be made through an educational campaign to develop understanding of the law by the public and the medical profession.

The following year the agencies again petitioned the Committee for help, this time in an effort to reach obstetricians for discussion of the problem. The Committee replied with a suggestion that a broad study be made. The result of this suggestion was a year-long study by a special New York City Committee on Adoptions organized under the auspices of the Academy of Medicine, the United Hospital Fund and the Welfare Council (now the Community Council).

In its report published in 1948 the Committee on Adoptions formulated four principles which it believed should be embodied in any new legislation on independent adoptions; that is, adoptions arranged by others than agencies. These principles were:

1. Notification of an appropriate public welfare agency by adoptive parents within two weeks after a child is received in their home.
2. Prompt investigation by an appropriate social agency of the placement of the child in a prospective adoption home; this investigation shall be a requirement for a petition to the court for adoption.
3. Procedures for the termination of placements unsatisfactory for adoption.
4. Prevention of the placement of children for profit by penalties or otherwise.

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* Report prepared by Subcommittee on Adoptions, comprised of: Alfred E. Fischer, M.D., Chairman; Robert C. Austrian, M.D.; Linn J. Boyd, M.D.; Milton D. Klein, M.D.; Bernard J. Pisani, M.D.; Philip M. Stimson, M.D.; H. D. Kruse, M.D., Secretary.

** Adopted by the Committee on Public Health, The New York Academy of Medicine, April 4, 1960.

A new aspect of the subject of adoptions has just been raised by the Committee on Adoptions of the Community Council of Greater New York, which proposes to enlist the interest of key medical and hospital organizations in New York City in encouraging physicians and hospital personnel to cooperate with recognized child-placing agencies rather than to carry out placements independently.

As a guide to medical societies in developing policy statements, the Community Council's committee has recommended a statement adopted by the Medical Society of the State of North Carolina in 1956.

Pointing out that "adoption is a highly specialized process which involves the exercise of social work skills", the statement urges: 1) that all county medical societies carefully scrutinize any practice that may lead to the placement or referral by a physician of any child for adoption, and 2) that individual physicians acquaint their patients who intend to have their children adopted with the proper procedures as prescribed by law and encourage the mothers to contact promptly the authorized social agencies.

A similar statement defining the role of the hospital in adoptions was approved in 1958 by the Hospital Council of Maryland. Hospitals were urged to provide information concerning services for unwed mothers and to make a strict regulation that staff members should not carry out adoption procedures without participation of the hospital social service or a community agency.

Dr. Samuel Karelitz, chairman of the Community Council's Committee on Adoptions and also of the Committee on Adoptions of the American Academy of Pediatrics, appeared before the Executive Committee on February 29. He explained that his Community Council committee is a local segment of a statewide group which is studying adoption laws and practices in New York State. It is urging that infants offered for adoption be placed only through agencies, and Dr. Karelitz requested the cooperation of the Committee on Public Health.

Dr. Karelitz emphasized the vast amount of work necessary in the management of unwed mothers and their infants. As examples of difficult problems he cited the placement of older children, handicapped children, non-white children and those of an inter-racial background. His conclusion was that since adoption requires the services of trained people from various disciplines, physicians should call on the specially qualified agencies rather than attempt to handle these complicated and difficult procedures themselves. This is particularly feasible in New York City, he observed, because this city has adoption agencies of the highest caliber to be found in the world.

The current concern with adoption practices does not arise from the threat of the black market, as did the concern in 1945 and 1946. Present laws are believed to be adequate to control the unsavory business of buying and selling babies. Rather, the present movement appears to be an effort on the part of the adoption agencies to have all adoptions pass through their hands.

According to the Community Council's committee, fewer children are returned after placement by recognized adoption agencies than when placement has been made independently by an individual. It was the conviction of that committee that

only an agency set up for the purpose could handle the difficult cases satisfactorily.

Having reviewed the situation in New York City and having studied the principles formulated by the Medical Society of the State of North Carolina and by the Hospital Council of Maryland, the Committee submits the following recommendations concerning the physician's relations to adoption of newborn infants of unwed mothers:

1. The Committee on Public Health of The New York Academy of Medicine urges that physicians be instructed in sound adoption practices and in the use of social agencies or the social service departments of their hospitals, which are trained to carry out this function.

2. The Committee recommends that every physician who attends an unwed mother before or at the birth of her child make known to her the community services available to her whether or not she wishes to place the child for adoption.

3. The Committee is of the opinion that physicians should limit their own services to an unwed mother to rendering the medical care she or her child needs.

4. The Committee advises that physicians should not go beyond this point of informing the unwed mother of the available community services and of providing medical care. They should not participate further in the adoption procedures.

ISAAC WOOD, M.D., 1793-1868

The Academy's Fourth President

The following sketch appeared as an obituary in the *Medical Register of the City of New York and Vicinity*, New York, 1868, pp. 339-341. For another account and his portrait, see pp. 632-4 of the September, 1960 issue of this *Bulletin*.

Isaac Wood, the fourth son and sixth child of Samuel Wood, a widely known book-dealer, and one of the founders of the present publishing house of William Wood & Co., was born August 21, 1793, in Clinton Town, Nine Partners, Dutchess County, N. Y. His father died in his eighty-fourth, and his mother (Mary Searing) in her ninety-first year.

The removal of his parents to the city in 1803, enabled our physician of the future to enlarge the sphere of his opportunities for mental improvement, and it was only through a great desire to enter the ranks of the profession as speedily as possible that he abandoned his original intention of completing his classical studies by a collegiate course. He, accordingly, duly entered the office of Dr. Valentine Seaman, in his 18th year.

He served the New York Hospital, as a member of the Resident Staff on the surgical side, for two years, one-half of the term being previous to June, 1815, the date of his license from the Medical Society of the State of New York. As a member of the same class with Joseph R. Drake, the poet and wit, and Bern. W. Budd, the eminent conchologist, he received his diploma, in 1816, from "Queen's College Medical Department in the City of New York."

Having joined the Medical Society of the County of New York, January 10, 1820, he displayed his modest little sign from his father's residence, No. 29 Rose Street. The lapse of two years find him at No. 12 Cherry Street, where, excepting the brief interval represented by a portion of his service at Bellevue, he remained until 1835, at which time, according to the Directory of that year, his address became 335 Pearl Street. This was in the neighborhood of Peck Slip. From the latter locality he went to East Broadway, a street, from its great number of physicians, once popularly known as "Doctors' Row." His residence here extended from 1840 to about 1857, when he followed the general movement "up-town."

Dr. Wood's desire to fill up every moment of his time with charitable offices prompted him to accept many positions which taxed his energies without yielding any immediate, or at the best, adequate pecuniary returns. Among these may be mentioned that of Consulting Accoucher to the Out-Door Lying-In Charity for the Second Ward, Member of the Society of the New York Hosiptal, and the more arduous relation of Member of the Society for the Reformation of Juvenile Delinquents. A strong believer in combined effort, his short slender figure was a familiar object at every association promising to advance the cause of science, edu-

cation or humanity. His success in organization was remarkable, and to him, both the Academy of Medicine and the Society for the Relief of the Widows and Orphans of Medical Men, owe much that is excellent in plan and admirable in working. This may be said without any disparagement to the efforts of Dr. Delafield, to whom, in the case of the latter association, the credit of having made the first proposal of its institution, justly belongs.

His connection with the American Bible Society, the N. Y. Institution for the Blind, and most of the benevolent projects of the day, together with the interest manifested by him in the cause of public education, might be further adduced as corroborative evidence in favor of his broad humanitarian views.

Adding steadily to his reputation for probity and reliability, he was appointed, April 14, 1825, by a committee of the Common Council, to investigate the causes, etc., of the disease (typhus fever) then a fearful epidemic at the Penitentiary, his colleagues being Drs. Joseph Bailey, Joseph M. Smith, and Stephen Brown, now all deceased. This duty discharged, he accepted the position of Consulting Physician to this Institution and to the Alms-house. The demands upon his time being now quite heavy, he was forced to resign from the City Dispensary on December 19th of the same year, but before the close of the first month of the following year he might have been found busily correcting abuses as the Resident Physician of the Alms-house and Penitentiary. Among the reforms which he instituted were the collection and separation of the pauper lunatics from the rest of the city poor. The medical government of this now magnificent city charity, projected in 1811, and opened for the reception of inmates five years afterwards, was, before Dr. Woods' accession to office, intrusted to a Visiting or Consulting Physician, while the responsible duties were really performed by one or two physicians resident upon the premises. Conscientious from principle and benevolent by impulse, he could not well escape the eulogy of the warm-hearted, charming author of "Old New York," who characterizes the seven years' administration of affairs by Dr. Wood as having been conducted with "signal benefit to the public interests and to humanity." It may also be remarked that this period included "the great cholera year" of 1832, and that our physician himself contracted the disease while in the line of duty. This attack precipitated his resignation, as it prostrated his energies to such a degree that he did not consider himself fully restored to his former vigor until after the lapse of five years.

Dr. Wood was the President of the "Kappa Lambda Society of Hippocrates" in 1845, of the Medical Society of the County of New York in 1846, and of The N. Y. Academy of Medicine in 1850 and 1853. He was also Treasurer of the American Medical Association, but served only one term.

Dr. Wood died at Norwalk, Conn., March 25, 1868, of double pneumonia. His funeral took place from the Friends' Meeting House in Twentieth Street, near Gamercy Park.

He was thrice married, and the father of four children; of these a son alone remains. His only daughter was the wife of Dr. Thomas F. Cock.

NEW YORK PATHOLOGICAL SOCIETY

ABSTRACTS OF PAPERS AND DISCUSSION

Presented at the Meeting on February 25, 1960, at The New York Academy of Medicine

Hepatic Cancer; Primary and Secondary

EDWARD A. GALL

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A brief consideration is given to certain anomalous hepatic lesions which, on occasion, represent the source of peculiar embryonal neoplasms with mixed structure, encountered in childhood. Cursory remarks are made in respect to vascular neoplasms and hepatic manifestations of malignant lymphoma. Circumscribed inflammatory nodules (gumma, pseudohepatoma), which may be mistaken for neoplasms, are illustrated.

The bulk of the presentation is concerned with the incidence of both primary and metastatic carcinoma of the liver at the Cincinnati General Hospital over a 38-year period (1921 to 1958)[1]. As a preliminary, a working classification of cirrhosis is developed. The terminology proposed comprises posthepatitic (217 cases), postnecrotic (69 cases), nutritional (161 cases), mixed (86 cases), obstructive (biliary) (71 cases), congestive (cardiac) (51 cases) and pigmentary (27 cases) cirrhosis. Criteria for distinction and a conceptual schema of pathogenesis are discussed.

An analysis of the relationship of cirrhosis and 96 selected examples of primary liver cancer is delineated. In only 58 of these (60 per cent) were the two conditions coincident. The occurrence rate among the 682 examples of moderate to severe cirrhosis was 8.5 per cent; this is twice that commonly recorded in the Occident. However, if one carried out the calculations against all cases of cirrhosis catalogued (1250), regardless of degree of fibrosis and distortion, the rate proved to be 4.3 per cent.

Sixty-four per cent of the hepatomas were accompanied by cirrhosis. When this was reconsidered in the light of the type of cirrhosis, a salient variation became manifest. This neoplasm had an incidence of 13 per cent and 20 per cent respectively in posthepatitic and postnecrotic cirrhosis. It was particularly noteworthy that nutritional cirrhosis, comprising 24 per cent of the group, had an exceedingly low incidence (1.2 per cent). This was probably not much in excess of the incidence of hepatoma in noncirrhotic livers.

In the case of cholangiomas, on the other hand, 45 per cent were associated with cirrhosis. Upon analysis of concomitance in relation to the type of cirrhosis, another disproportion became evident; the great majority with combined cholangioma and cirrhosis (78 per cent) occurred in the biliary (obstructive) form. Indeed, in almost all of these, there was reason to believe that the cirrhosis was in good measure attributable to the obstructive qualities of the neoplasm itself. It appeared, therefore, that cholangioma constituted no hazard as a sequela of cirrhosis.

Among the 682 instances of cirrhosis, 108 (16 per cent) were found to be accompanied by a primary neoplasm arising in an extrahepatic site. By selection, these were only neoplasms with the potentiality for hepatic metastasis. In 29 cases (4.2

per cent), metastasis to the cirrhotic liver had actually occurred. In a control survey, 1,000 necropsy cases (1955-1956) of comparable age but without cirrhosis were also investigated. There were 218 examples of extrahepatic primary cancer (21 per cent), in 101 of which (10 per cent) liver involvement was encountered.

Giving consideration to the type of cirrhosis affected by metastasis, however, it was found that among the 71 instances of biliary (obstructive) cirrhosis, metastatic neoplasm was manifest in 22 (31 per cent). In the remaining 611 cases of nonobstructive cirrhosis, there were only seven examples of metastasis (1.0 per cent). It appeared, therefore, that in the latter group the susceptibility to metastatic carcinoma was strikingly reduced. It does not follow, however, that the liver, which is the seat of obstructive cirrhosis, is necessarily more susceptible to this circumstance. A critical evaluation here indicated that in almost all instances the obstruction engendering the cirrhosis was induced by the extrahepatic cancer (pancreas, bile duct, gall bladder), which had itself been the source of the metastasis.

CONCLUSIONS

1. Primary hepatic carcinoma appeared as a complication in 8.5 per cent of the cases with significant degrees of cirrhosis at the Cincinnati General Hospital.

2. The highest incidence of hepatoma was in posthepatitic and postnecrotic cirrhosis (13 and 20 per cent). The lowest incidence (1.2 per cent) was in nutritional cirrhosis. In the latter condition hepatoma appeared to be little more common than in cases without cirrhosis.

3. Cholangioma accompanying cirrhosis, on the other hand, occurred in the main with obstructive (biliary) cirrhosis. Indeed, there was evidence to indicate that in most instances the cirrhosis here had been caused by the obstructive qualities of the cholangioma.

4. Metastatic carcinoma to the cirrhotic liver was encountered in 4.2 per cent of those cases in which primary extrahepatic cancer existed simultaneously. In a control group of 1,000 cases without cirrhosis, the incidence of liver metastasis from an extrahepatic source was 10 per cent.

5. Among the cases of cirrhosis with metastasis, the incidence in obstructive cirrhosis was 31 per cent; it was only 1 per cent among the remaining forms.

6. Susceptibility to metastatic neoplasm appeared to be reduced in the cirrhotic liver. Susceptibility in biliary cirrhosis was apparent only, since, in most instances, the hepatic fibrosis appeared to result from obstruction caused by the extrahepatic cancer.

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DISCUSSION

JOHN M. PEARCE: As you know, I have had a long association with the New York Pathological Society, and am greatly concerned with it; therefore I was tremendously pleased when I was asked to discuss the paper of Dr. Gall. I have also had a long association with Dr. Gall's work, but I don't think I can discuss it adequately. I have been tremendously interested in what he had to say. I have one question that I should like to pose to the audience as a whole, and to Dr. Gall, and that is, is it his conclusion that carcinoma of the liver is much commoner in the posthepatitic and postnecrotic cirrhosis than in the so-called nutritional cirrhosis? I ask that question because all of us through the World War II years noticed that there was a great epidemic, especially in the Pacific, of viral hepatitis, and a great many sequelae came from it. The epidemic which occurred then has continued in the United States. Yet, as far as I know, the incidence of carcinoma of the liver has not increased. There has not been an increase anything like that of carcinoma of the bronchus, which we have all seen. That is one thing that I should like to ask, if carcinoma is much commoner in the posthepatitic and postnecrotic liver, why? The other question that occurred to me, which is a little hard to explain, is the fact that metastatic carcinoma does not

occur frequently in the cirrhotic liver. My idea would be that the blood flow to the cirrhotic liver is not so large as to the non-cirrhotic liver. I do not know much about this, so I am not going to go on about it, but I want to thank Dr. Gall for his very interesting talk.

H. M. ZIMMERMAN: If Dr. Pearce was hesitant to discuss the paper, I am hoping that the next person I shall call on for a comment will be less hesitant; to me, at least in this Society, liver and Popper are synonymous terms, and I would like to have Dr. Popper carry on the discussion.

HANS POPPER: Dr. Gall's masterful presentation raises a great many questions of interest to a pathologist. I should like to ask a few, to give him a chance to elaborate on his viewpoints. The first question deals with the specimen which shows microcystic alterations in many portal tracts. We also see them frequently, and usually consider them as functionally insignificant developmental defects of hamartomatous character. Exceptionally they seem to become a clinical problem in that they are found in patients with portal hypertension, not explained by other pathologic features. We have several such cases in our files. In one instance, the patient died from esophageal hemorrhage. I wonder what Dr. Gall's experience has been with such lesions. I am not quite sure whether such microcystic changes or Meyenberg complexes are always developmental defects or whether they are acquired, possibly inflammatory lesions. The same holds true of ductal proliferations in the pancreas. Similar lesions are seen in the liver of animals on carcinogenic regimes.

Another question which I should like to ask, in order to take advantage of Dr. Gall's experience, deals with hemangiomas in the liver. In our material, both in New York and in Chicago, we saw them frequently in adults and seldom in children. Do you believe that cavernous hemangiomas are the result of developmental defects or are they acquired lesions developing later in life, possibly under the influence of steroids?

I should also wonder how many of the cases you designate as posthepatitic cirrhosis were observed in alcoholic patients. I fully agree with Dr. Gall that primary hepatic cancer occurs with particular frequency in postnecrotic cirrhosis, or what he calls posthepatitic cirrhosis. However, in our experience, many of the patients with primary hepatic cancer have an alcoholic history, and I wonder whether the alcohol abuse is not related to this postnecrotic cirrhosis.

Finally, I should like to ask whether he believes that the frequent association between posthepatitic cirrhosis and cancer is the result of an alteration or mutation produced at the time of the acute viral hepatitis, or is related to excessive regeneration in the cirrhotic stage.

E. D. GALL: Dr. Pearce and Dr. Popper, thank you for your courteous and gracious compliments. As to an increasing incidence of primary carcinoma of the liver, I know of two salient facts at the moment: one is a recent report by Dick McDonald at the Boston City Hospital indicating that there has been a significant increase in the occurrence of hepatoma at that hospital in recent years; in our own hospital group we have encountered 24 cases of primary liver cancer in the last two years. How this will level off I do not know, but there certainly appears to be a rising trend. In my Residency years this was a rare group of tumors; it is by no means an uncommon lesion at the present time, either among our autopsies or in our surgical pathology service.

Whether a reduction of blood circulation in the cirrhotic liver represents the basis for a reduction in susceptibility to metastatic cancer, I have no clear idea. That is one of the many reasons that may be offered in explanation for it. I did not want to spend too much time in reviewing all of the ramifications I have gone through in attempting an explanation for the curious resistance to liver metastasis in cirrhosis.

I want to raise one note of warning; I am sure I do not have to make the point for Dr. Popper. One must be cautious in necessarily relating esophageal varices to portal hypertension. Five per cent of our

cases of varices, many of them with massive hemorrhage, were unassociated with portal hypertension. I have not seen portal hypertension in congenital cystic disease of the type I demonstrated. I have seen it in the liver massively replaced by cystic disease. The lesions I showed were representative of an early phase or a *forme fruste*. We have had one instance of portal hypertension among three instances of advanced congenital cystic disorder in the liver. I confess I cannot with clarity distinguish between the congenital lesion and the Meyenberg plexus, which might be a sequel of burned-out biliary duct obstruction. When there is spotty intrahepatic ductal obstruction, the end picture looks very much the same. With the distribution shown in the illustrations I demonstrated to you, I believe there is little question that a congenital malformation exists. Indeed, it was in that instance associated with polycystic disease of the kidney. The mechanism of the production of these cysts is as mysterious in the liver as in the kidney.

I agree with Dr. Popper that we do not see hemangiomas of the liver in children with the same frequency they are encountered in adults. This might well be an argument against their representing malformation. Our diagnostic file lists them in the category of neoplasm. Once the cases are catalogued there seems to be an immutability.

How many of our patients with postnecrotic cirrhosis and posthepatitic cirrhosis are alcoholics? I would say offhand that in one hospital it might well run higher than 60 per cent. I wish you had asked another question, though. How many in our over-all adult hospital population are "alcoholic"? I set two Residents to work on this survey; later, I put two instructors on it, then an Associate Professor, and finally I took up the analysis myself. Taking an acceptable standard, which would exceed the alcoholic consumption of the average pathologist, 40 per cent of our hospital population could be listed as "alcoholic". Thus, the co-existence of alcoholism and cirrhosis may be simply coincidence. I am sure the figure would be much lower in a private hospital but I have no ready thought as to whether cirrhosis is as common in such institutions.

Dr. Popper asks whether the virus of hepatitis is the trigger which fires off hepatoma fifteen years later. I think I shall not take the bait proffered. The question of relationship between virus and neoplasm certainly transcends the limited sphere of hepatic cancer.

*A Study of Certain Microscopic Features in Regional Enteritis, and Their Possible Prognostic Significance**

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In a histologic study of 56 cases of regional enteritis, it was found that "aberrant pyloric glands" occurred in 58.9 per cent; "epithelioid and giant cell granulomata" in 37.5 per cent; "neuromatous" lesions in 14.3 per cent, and vascular arterial lesions in 16.1 per cent of the specimens examined.

No satisfactory clinical-pathologic correlation could be established between these histologic lesions and prognosis, in terms of postoperative recurrences after a minimum five-year follow-up period.

The pathogenesis and the specificity of these four histologic lesions are not clear. The "aberrant pyloric glands" are quite likely an acquired rather than a congenital lesion. They may represent an adaptation of the intestinal mucosa to an abnormal environment.

In this series, the granulomatous lesions were never associated with systemic sarcoidosis, or with demonstrable acid-fast bacteria or fungi.

The "neuromatous" lesions are probably an acquired, diffuse hyperplasia of the myenteric neural system, almost certainly different from the common amputation neuroma.

The occasional vascular arterial lesions observed in this series of cases appeared to be non-specific responses to inflammation, secondary to the chronic ulcerative disease.

It appears that none of these histologic lesions is pathognomonic for the entity known as regional enteritis.

DISCUSSION

H. M. ZIMMERMAN: When we talk about regional ileitis we cannot help but mention the name of Crohn. When we were faced with asking someone to discuss Dr. Lattes' paper this evening, we selected our favorite surgeon and physiologist, Samuel Standard, to start the discussion. We were on the verge of asking Dr. Crohn to do this, and in view of the newspaper release of two days ago you will understand how fortunate we were not to have done so. Had he accepted, he undoubtedly would have been more fortunate, for he then might have been here and not in jail in India! Will you start the discussion, Dr. Standard?

SAMUEL STANDARD: The pathologist tells us what the diseased tissues look like, how they got that way, what the cause may have been and how it has progressed. The surgeon, armed with this knowledge, must say how he encounters the disease, what it does to the host that harbors it, how he has learned to treat it, and what is the result of treatment. Let us begin where we should end this discussion. Knowing the end, we may look upon the recognition, development and progress in our understanding of this disease with a clearer eye. This is the sad truth,—two-thirds of the cases of regional enteritis come to surgery. In two-thirds of those operated upon there is recurrence after operation. This is the best we have been able to achieve in the treatment of this disease!

With this in mind, the drama of its discovery, the subtle internecine warfare of priority in discovery, the immodest proclamations dealing with nomenclature, take on a childish game-like quality instead of a forthright effort at elucidation such as has been attempted by Dr. Lattes tonight. How different is this painstaking effort to find some specific entity in the pathologic picture of the disease from the wooden-sword fencing of the past.

Dr. Leon Ginzburg, a young surgeon

* Abstract of article, dealing in detail with this study, which will appear in *Gastroenterology*, under the same title, under the joint authorship of J. Antonius, F. Gump, R. Lattes, and M. Lepore.

working in Dr. Klemperer's pathological laboratory at Mount Sinai Hospital, was the first to separate the disease entity now known as regional enteritis from the many non-specific granulomata and the specific tuberculous granulomata of the intestinal tract. In 1932, with Crohn and Oppenheimer, the first 13 cases of this entity came to publication.[1] It was in that paper that regional enteritis was launched on its own orbit. There was general rejoicing that it was removed from the disease tuberculosis, a dread disease then, a still dreaded if less lethal disease now. Today, with the newer antibiotic and chemotherapeutic control of tuberculosis, we should perhaps wish to put regional enteritis back in the tuberculosis group, but Pandora's Box has been opened, the genie released, and we can't get him back and slam the lid down. Regional enteritis today is a less predictably curable disease than tuberculosis.

Historically, Thorek's[2] insistence that Combes in 1806[3] was the first to discover the disease, and his insistence that Crohn, Ginzburg and Oppenheimer rediscovered it in 1932, belongs with the talmudists' effort to determine the angel capacity of a pinhead. (Actually, Combes reported one autopsied case which may or may not have been this disease.) Suffice it to say that of a series of 600 cases reported from the Mayo Clinic in 1954,[4] 40 appeared before 1932 and 560 after that date. In nomenclature, too, it has undergone some changes. The original paper was titled "terminal ileitis"; this was later changed to "regional ileitis"; Bargen's suggestion of "regional enteritis" covers all the possibilities of location in small and large intestine and is its present name. Statistically, 90 per cent of the cases appear in the terminal ileum; the present name covers the 10 per cent in which it appears in other locations. The nomenclatural changes have not altered the prognosis.

The clinical picture, so well described in the original paper, remains unchanged to date. Dr. Lattes has covered this, as well as the search for an etiologic factor so far unknown, and a review of the pathogenesis of origin and spread by lymphatic block, explaining the skip lesions and the sources of recurrence.

Claude Bernard insisted that his students tell him what they saw. Before any theory of where the lesion came from and where it was going, he wanted to know first exactly what they saw. Only if they saw clearly could they theorize clearly. Dr. Lattes has sought to see clearly. The enormity of the job he undertook in determining the four factors he sought is barely evident in the clear presentation of the material. The care and precise search he undertook leave no need for future repetition of this aspect of the pathologic picture of the disease. It may now be said that because of his effort the abnormal pyloric glands, the epithelioid and giant cell granulomata, the so-called neuromatous lesions and the vascular lesion are not pathognomonic of this disease.

His interesting speculation on the origin of the abnormal pyloric glands as heterotopic or metaplastic recalls to mind the work of John Sutton[5], who demonstrated, following cholecystectomy in the dog, remarkable metaplasia of the cuboidal cells, lining the common duct, to the villose, fronded, delicate, complexly branched epithelium seen in the gall bladder. Teleologically this may represent an effort to replace the absorptive surface lost with cholecystectomy. I have not seen this demonstrated in man, but if true, it may explain the new gall stone formation seen in ducts after cholecystectomy. Many of these may represent overlooked stones, but if the duct becomes a site of bile concentration, stone precipitation may be expected. This is true metaplasia.

A word about surgical therapy, since this may have been the reason for inviting me to this meeting:

1. There is complete agreement that the asymptomatic patient, in whom there is demonstration of the disease merely by x-ray, should be left severely alone.

2. When, at operation, an acute, fiery red, rubber hose segment of ileum is encountered, this should be left behind without surgery. Many of these lesions are completely reversible and may not recur.

3. It is sometimes difficult to decide whether appendectomy should be done in the course of surgery for regional enteritis.

When there is no involvement of the ileocecal area or cecum it is a safe procedure, and the removal of the appendix makes more simple subsequent diagnoses of ileitis which may be mistaken for appendicitis. In the presence of disease in the area of the appendix, its removal may lead to intractable fistulae and appendectomy should not be done.

4. In the presence of chronic, obstructive disease without acute involvement, resection and ileotransverse colostomy will prove a safe procedure. In a severely sick patient with existing acute disease, sidetracking with exclusion is the safer procedure. Sidetracking without exclusion should be avoided. (This, despite the excellent result achieved in President Eisenhower's operation.) A sidetracking procedure with exclusion, if followed by recurrence, can be supplemented by resection at a subsequent procedure. A point to bear in mind is that recurrent symptoms may mean colonic involvement, not ileal recurrence.

To end where we began,—with good judgment and creditable surgery and aftercare, almost two-thirds of the patients have recurrence, and require further surgery. Regional enteritis continues to remain in the category of "unsolved" disease.

PAUL KLEMPERER: Dr. Standard's discussion encourages me to make a few remarks. Up to 1932 when the first report came from our hospital, I had seen only one case at autopsy before, and that was in Europe. I always wondered what happened in those cases which must have existed but did not come to operation. Did they heal spontaneously? I once saw a case in which no resection was done, but only an anastomosis. The patient died two years later of an intercurrent disease. At autopsy the sidetracked ileum was perfectly normal. I wonder if Dr. Lattes has any correlation between the histologic picture and the subsequent events in those cases of ileitis in which the colon is also involved.

RAFFAELE LATTES: Thank you, Dr. Standard, for your discussion. I do not think we can solve here the question of "pyloric" metaplasia vs. heterotopia. Only one thing can be said: the only well-documented acceptable cases in which heterotopic gastric mucosa was found in the small intestine, in the absence of symptoms or signs of regional enteritis, were cases in which a fundic type of mucosa was found, and they were practically always either in Meckel's diverticula or in small polyps. The changes described tonight were those of the small intestinal mucosa differentiating into a pyloric type of mucosa. This was true with one exception, which was so exceptional that I would rather not discuss it here.

Dr. Klemperer brought up an extremely important point: what happens to patients with acute ileitis? I do not know whether I quoted correctly the clinical findings of Dr. Gump, but I believe that in our clinical series the great majority of patients with symptoms of acute terminal segmental ileitis who were explored, and in whom a swollen, edematous bowel wall was found, and in whom no resection or other surgery was performed, did not go on to develop the chronic disease.

As for colon involvement in this study, I did not include any instances of so-called ileo-colitis or segmental colitis, of which we have a very few. I believe there does exist a segmental lesion in the colon which anatomically, grossly and microscopically has a great resemblance to the regional enteritis of the small intestine, but we did not include examples of this lesion, and we have too few of them to be able to run a clinical analysis.

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NEW YORK HEART ASSOCIATION

Scientific Session Held at The New York Academy of Medicine, April 20, 1960

ABSTRACTS OF PAPERS SUBMITTED FOR PRESENTATION

(Part II)

Bridging of Interrupted A-V Conduction in Experimental Chronic Complete Heart Block by Electronic Means (Abstract)*

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The introduction of external pacemakers, isoproterenol hydrochloride and steroids, has greatly influenced the immediate prognosis of patients with acquired complete heart block and Adams-Stokes episodes. The long range prognosis has remained unsatisfactory in spite of the newly introduced therapeutic modalities. The transthoracic introduction of electrode wire or the introduction of a catheter electrode for direct stimulation are, in our experience, of limited usefulness in special situations. With presently available pacemakers and techniques, the rate of stimulation is variable but fixed at any given time. Experiments were undertaken to explore the feasibility of restoring atrioventricular conduction, its technical and biological parameters, and thereby restore autonomic control to cardiac dynamics. For practical purposes, the latter is mediated primarily through the S-A node: bradycardia with rest and cardiac acceleration with increased demand for cardiac output.

Chronic complete heart block was produced in mongrel dogs (15-25 Kg.) by placement, under direct vision by means of intermittent cardiac inflow occlusion technique, of a silk suture-ligature around the bundle of His. Two small circular tantalum-mesh electrodes were sutured to the right atrial surface close to the superior vena cava. A third, larger one, was attached to the right ventricular wall. Braided wires interwoven in the electrodes and insulated were brought out through the chest incision, with an indifferent electrode in the subcutaneous tissues of the wound.

Electronic bridging was successfully accomplished: bipolar atrial complexes were amplified and shaped to trigger, with an appropriate time delay ("P-R interval"), a physiological stimulator. All experiments were performed after recovery from surgery and without anesthesia. Rheobase and chronaxie of the ventricular myocardium have been determined. Adams-Stokes seizures have been experimentally reproduced and factors favoring and preventing it have been analyzed. A compact transistorized instrument has been constructed, applicable to humans, in which have been incorporated automatic safety devices (atrial tachy- or bradycardias).

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Prolonged Veno-Veno Pumping with Oxygenation (Abstract)*

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Prolonged veno-veno pumping with oxygenation is being studied in normal dogs and in dogs made temporarily cyanotic. For this to be successful, two conditions must be satisfactorily met: prolonged perfusion, and adequate increased oxygenation.

Venous blood is drained from a Teflon catheter inserted through a femoral vein up to the level of the diaphragm. Blood is drained directly into the Kay-Cross oxygenator and oxygenated blood is returned through a catheter placed in the right jugular vein. One thousand ml. per minute can be drained using two number 6 catheters, and 500-600 ml. per minute using one. With this technique, dogs have been successfully perfused continuously up to ten hours. The plasma hemoglobin was low in many cases and unusually high in some. Even those animals which had plasma hemoglobin values up to two grams, did well, had no elevation of BUN, and in four days the plasma hemoglobin levels were normal.

Cyanosis was created by placing the dog on a mechanical respirator and respiring the animal with a poorly oxygenated mixture, such as 5 per cent or 12 per cent oxygen in nitrogen. Preliminary studies have shown that the arterial oxygen of a cyanotic dog can be increased by 20 per cent to 40 per cent, when carrying out veno-veno pumping of 600 ml. per minute with oxygenation. Further studies are being carried out to determine the flow per minute required to improve the arterial oxygen saturation of a cyanotic dog, to levels compatible with life.

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The Differentiation of Two Spectra of Lesions: Pulmonic Stenosis, Intraventricular Septal Defect with Overriding Aorta; and Pulmonic Stenosis, Interventricular Septal Defect with Normal Aortic Root (Abstract)*

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The older literature distinguished between pulmonic stenosis (PS), interventricular septal defect (IVSD) with normal aortic root, and partially transposed aortic root (Tetralogy of Fallot). In recent years there has been an emphasis in classifying these within a single spectrum of lesions. This report presents evidence to support the thesis that there are two distinct groups of lesions.

In Tetralogy of Fallot the right ventricle (RV) communicates directly with the systemic circulation and therefore the left ventricle (LV) never assumes its normal role. In the group with normal aortic root

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the LV is hyperdynamic and shows evidence of hypertrophy. It is this hemodynamic distinction which allows their differential diagnosis, whether they are cyanotic or acyanotic.

Tetralogy of Fallot is a right-sided lesion, with catheter data that reveals balanced systemic and RV pressures and pulmonary artery (PA) pressures that are normal or below normal. Angiocardiogram reveals simultaneous and equal filling of the PA and aorta. The base of the aorta appears wider and more anterior than in normals. The group with normal aortic root reveals: 1) a giant 'A' wave in right atrial curves and in the neck veins (a finding not observed in those with Fallot's); 2) equal pressures in the systemic circulation and the RV, or slightly lower pressures in the RV; 3) PA pressures that are normal or slightly above normal; 4) angiocardiogram showing a normal size and position of the aortic root.

Some patients with normal aortic root, presented initially only as VSDs, have demonstrated progressive hypertrophy of the infundibular area (three in our series). Tetralogy of Fallot does not show progressive changes and, in a way, is a persistence of the fetal circulation. The normal root group does show clinical and physiologic changes with time. Postoperatively it has been found that the Fallot hearts become larger. In the normal aortic root group the heart would be expected to become gradually smaller. This latter speculation awaits verification by longer postoperative follow-up.

This study is based on 16 Fallots and 12 normal root group cases.

Influence of the Wedged Catheter Tip Position on Left Atrial Pressure Transmission as Demonstrated Arteriographically (Abstract)*

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During the course of right heart catheterization of 65 patients with congenital or acquired heart disease, wedged pulmonary arteriographs were exposed and wedge pressures and pulmonary artery pressures recorded. The wedge pulmonary arteriogram clearly delineates the relationship of the catheter tip to the wedged pulmonary artery. Such arteriograms show that where the usual clinical criteria for the wedge position of the catheter tip are satisfied, the catheter tip may assume any one of five positions in the wedged pulmonary artery. The catheter tip can wedge in: 1) an artery having a common axis with, and just smaller than the catheter tip (position I); 2) the tip may stop at a bifurcation of the artery (position II); 3) the tip may impinge against the wall of an artery at a sharp angle (position III); 4) the tip may position at the origin of three or more branches of the artery (position IV); or 5) the tip may lie unwedged in an artery with a larger diameter than the catheter (position V).

The catheter tip assumed position I in 24 of the 65 cases, and of this number 17 (71 per cent) yielded phasic pressure tracings. Position II was identified in 23 cases, 16 (70 per cent) of which were again phasic. Position III was noted in 13 cases, of which only 2 (15 per cent) were phasic, and an additional three tracings were phasic

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only in a certain stage of the respiratory cycle. Position IV occurred in 4 cases with 3 (75 per cent) of these giving phasic tracings. In one case, position V was found, and this did not reflect the left atrial pulse.

Left atrial pulse transmission was influenced by the radiopaque dye injection. Repeat wedge tracings were done following the dye injection. Eighty-five per cent of the tracings which were phasic before the dye injection became damped and unphasic. This was presumably the result of vasoconstriction.

It is concluded that the position of the wedged catheter tip is a variable of importance in the satisfactory transmission of the left atrial pulse. Other factors influencing pressure transmission are discussed in the light of this finding.

Demonstration of Increased Proactivator in Induced Fibrinolytic States (Abstract)*

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The present concept of the fibrinolytic system is that plasminogen is converted to the fibrinolytic agent plasmin by a group of proteolytic substances (activators). Both plasmin and plasminogen activators possess lysine ester-splitting activity. Streptokinase lacks this activity, and its capacity to activate plasminogen results from its interaction with an inactive precursor (proactivator), producing an activator with esterase activity. Whether proactivator and plasminogen are separate substances is a controversial matter.

Epinephrine and electroconvulsive shock (ECS) have been shown to produce increased euglobulin fibrinolytic activity, resulting from an increase of plasminogen activation. Lysinemethyl esterase activity of the euglobulin fraction was not increased by these procedures, although such activity is characteristic of plasminogen activators. Esterase activity was significantly increased, however, in post-epinephrine and post-ECS specimens when streptokinase was added to the reaction mixture. Since streptokinase alone lacks this activity, these results indicate that euglobulin following epinephrine and ECS contains an increase in material activated by streptokinase, either proactivator or plasminogen. Further studies demonstrated that the material increased was not plasminogen. This material was assayed by conversion to plasmin and the activator used for this conversion removed either by acid precipitation or heat. Esterase activity of the activator-free plasmin was unchanged following epinephrine or ECS. It was consistent regardless of the activator used or the method of its removal, and was regularly less than that due to streptokinase when activator was not removed. These findings indicate that streptokinase-induced esterase is due to the conversion of both proactivator and plasminogen and that the former alone is increased by epinephrine and ECS. The findings also indicate the separate identities of these substances. The value of an artificial substrate, without clot lysis, in the measurement of these components of the fibrinolytic system is demonstrated.

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In Vitro Re-Utilization of Intracellular Cholesterol by Human Arterial Intimal Cells (Abstract)*

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Endothelial cells obtained from the intima of short-term organ cultures of the aorta and coronary vessels of patients with severe atherosclerosis were maintained in media containing aqueous microemulsions of C^{14}-cholesterol. After 72 hours of incubation the cells were rinsed in a balanced salt solution and transferred to a cholesterol-free medium.

It was observed that those cells which had high concentrations of intracellular cholesterol did not return to their initial state, but degenerated, and their protein-bound cholesterol was immediately incorporated by surrounding cells of the same type. This cyclical re-utilization would then continue until all endothelial cells were destroyed, unless it was inhibited by the addition of heparin or linoleic acid to the medium.

These results suggest that cholesterol re-utilization may play a role in atherosclerosis and could explain the clinical findings of atherosclerotic patients with normal cholesterolemia, since atherogenesis could continue independent of blood cholesterol levels once the initial arterial lesion had been produced.

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Effect of Cardiac Irradiation upon Myocardial Vascularity (Abstract)*

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The use of cardiac irradiation as a therapeutic means of increasing myocardial vascularity was investigated in a series of 96 dogs. Sixty-six dogs received cardiac irradiation during a two-week period. The calculated doses to the myocardium were 1300R, 2000R and 2500R. Thirty-six non-radiated dogs served as control subjects. In an attempt to evaluate the degree of protection that radiation may afford, all dogs were subjected to acute myocardial insult by ligation of the anterior descending coronary artery. The 24-hour mortality figures reveal a significant difference between radiated and control groups. Three of 30 control dogs (10.3 per cent), 8 of 25 (1300R) dogs (32 per cent) and 12 of 25 (2000R) dogs (48 per cent) survived ligation and were alive 24 hours later. To determine whether this protective effect was merely a transient phenomenon, 16 dogs were radiated and subjected to coronary ligation six months later. Twelve of 16 (75 per cent) dogs survived ligation.

Physiological, pathological and electrocardiographic studies were performed on surviving dogs at intervals up to six months' post-ligation. Peripheral coronary pressure and flow determinations measured distal to the coronary ligature revealed good retrograde flow and peripheral pressures among the radiated dogs at the time of ligation, with these values increasing in the post-

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ligation period. Barium and vinylite injection studies of the radiated hearts revealed the blood to flow in a retrograde fashion from intercoronary anastomoses between the ligated anterior descending coronary artery and the unoccluded branches of the remaining arterial tree. Comparison of equivalent radiated and control hearts subjected to coronary ligation revealed the radiated hearts to be more vascular. Pathological studies, gross and microscopic, revealed the presence of infarcted muscle, involving the entire thickness of the ventricular wall, in the control dogs. The radiated dogs, of equivalent survival periods, did not exhibit this through and through infarction but exhibited a spared area of varying degree of normal heart muscle in the subepicardium region throughout the extent of the infarction. Thus, it would seem that cardiac irradiation has induced sufficient vascularity to account for the differences noted in the survival, backflow and pathological studies.

Relationship of Rheumatic Fever Recurrence Rate per Streptococcal Infection to Clinical Features of the Patients (Abstract)*

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The attack rate of rheumatic fever after Group A streptococcal infections is known to be higher in patients with previous rheumatic attacks than in the general population. In these patients, the possible effect of some host factors on the outcome of streptococcal infections is uncertain and has been analyzed in the present study.

Four hundred and thirty-four children and adolescents who had had rheumatic fever were examined monthly over a five-year period, for 1608 patient-years. Monthly throat cultures and at least bi-monthly antibody determinations were done. Despite continuous antistreptococcal prophylaxis (sulfadiazine, repository penicillin, or oral penicillin), 267 Group A streptococcal infections occurred, which were associated, in 44 instances, with definite rheumatic recurrences.

Recurrences developed with 16 (9 per cent) of 175 infections in patients with no heart disease, and with 28 (30 per cent) of 92 infections in patients with heart disease at the time of the infection. Within the latter group, 20 infections occurred in patients with markedly enlarged hearts and 9 (45 per cent) led to rheumatic recurrences. The rheumatic fever recurrence rate per infection (RFRR/I) likewise increased with the number of previous attacks of rheumatic fever. It was 10, 23, 27 and 43 per cent in patients with one, two, three and four previous attacks respectively. This trend was detected despite the increase in age with number of attacks, and a decrease of RFRR/I with age (22, 21, 12, and 8 per cent in the 7-9, 10-12, 13-15 and 16-18 age groups). The RFRR/I also decreased with the time elapsed since the preceding rheumatic attack. It was 24, 16, 11, and 10 per cent in infections which occurred respectively 6-23, 24-41, 42-59 and 60+ months since the last rheumatic attack.

Contrary to expectation, the RFRR/I bore no relationship to the time elapsed since the preceding streptococcal infection.

These data indicate a relationship between the rheumatic fever recurrence rate per infection and certain underlying clinical features, which are independent of, and antedate, the streptococcal infections involved.

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Reflex Hemodynamic Changes Induced by Rapid Intra-Arterial Injection of Hypertonic and Hypotonic Solutions (Abstract)*

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The reactions of arterial pressure and heart rate to rapid femoral and brachial intra-arterial (IA) injection of 2-80 ml. of hypertonic and hypotonic solutions (saline and dextrose) were studied in 62 adult mongrel dogs under deep pentobarbital anesthesia. The IA injection of these substances in hypertonic solution (1.4 to 10 x hyperosmotic) characteristically provoked systolic and diastolic hypertension and tachycardia beginning 6-8 seconds after onset of injection and lasting from 2 to 30 minutes. A concomitant elevation of pressure within an isolated venous segment was also demonstrated. The magnitude of the pressor response increased with solutions of greater hypertonicity. Responses were seen occasionally with femoral IA injection of as little as 2 ml. of 5 per cent saline.

Isotonic solutions were without circulatory effect, as were distention of the artery or with mechanical trauma of the animal.

Hypotonic solutions produced slight hypotension. Temperature of the solutions and pH did not seem to be contributory.

Changes in central blood volume, cardiac distention or local vasomotor adjustments in the injected limb were excluded as factors in the primary response.

Ipsilateral sympathectomy T_{11}-L_4 did not eliminate the response. However, section of all peripheral nerves in the limb completely abolished responses. Spinal cord transsection at C_{1-2} and generalized sympathetic ganglionic blockade with tetraethylammonium also abolished responses. It is suggested that these hemodynamic reactions are initiated by osmotically sensitive peripheral receptors, and are mediated by a reflex whose afferent arc runs in the peripheral somatic nerves, and whose efferent pathway consists of the sympathetic nervous system.

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Hemodynamic Alterations in Experimental Myocardial Infarction with Shock and the Effects of Balloon Obstruction of the Abdominal Aorta and Closed-Chest Extracorporeal Circulation (Abstract)*

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The effects of extracorporeal circulatory support on coronary perfusion (central aortic) pressure, cardiac output, systemic vascular resistance, right atrial and left ventricular pressures were investigated in closed-chest dogs with shock following plastic sphere coronary embolization.

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Following coronary embolization, there was decline in aortic pressure and cardiac output, but little change in systemic vascular resistance. Shunting of large volumes of blood from the superior vena cava into the abdominal aorta failed to produce a rise in coronary perfusion pressure. To raise central aortic pressure by extracorporeal means, it was necessary to increase vascular resistance. This was accomplished by inflating a balloon catheter inserted via a femoral artery to the lowest point of the abdominal aorta at which inflation of the balloon produced a rise in central aortic pressure. Blood pumped from the superior vena cava supplied the distal aorta below the obstruction. This caused sustained increase in coronary perfusion pressure throughout the 4-hour duration of the experiments. Average mean central aortic pressure in 12 animals rose from 73 to 139 mm. Hg. There was some diminution in distal aortic pressure. Left ventricular diastolic and right atrial mean pressures remained normal. Left ventricular work did not change significantly despite a rise in central aortic pressure because of shunting of a portion of the venous return into the distal aorta. The sum of the superior vena cava shunt flow and the cardiac output exceeded the postembolic cardiac output prior to extracorporeal circulatory support, suggesting that increased coronary perfusion resulted in increased venous return and improved myocardial function.

It is concluded that failure of peripheral vascular resistance to rise sufficiently in response to reduction in cardiac output is of paramount importance in the development of shock following myocardial infarction. Vascular resistance and coronary perfusion can be mechanically increased by aortic obstruction. This method may prove beneficial in patients who do not respond to vasopressor agents.

Relation of Direction of Electrical Recovery to Right Ventricular Pressure in Atrial Septal Defect (Secundum Type) (Abstract)*

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Hemodynamic data in 37 patients with atrial septal defect proved by cardiac catheterization have been correlated with specific electrocardiographic abnormalities. Ranging in age from 1½ to 56 years, 22 of the patients were over the age of 13.

The left atrium was entered via the defect in 25 subjects, and a left to right shunt at an atrial level demonstrated in all. Partial anomalous pulmonary venous drainage to the right atrium was the only associated cardiac lesion allowed in the series. Those with a significant pressure gradient across the pulmonic and tricuspid valves were eliminated from the study.

Right ventricular pressures ranged from 15/3 to 95/5 mm. Hg. Twenty-two patients had normal pulmonary artery and right ventricular recordings. In nine the systolic pressures were greatly elevated. Values in the remaining 12 were minimally raised or at a borderline normal level.

Deviation of the mean electrical QRS axis was to the right in 28, normal in seven, and left in two cases. A right "bundle-branch block" pattern (rSR′ in lead V_1) was present in 30 patients. In some instances, recording the electrocardiogram at rapid speed was necessary to demonstrate clearly this morphology. The duration of QRS exceeded 0.12 second in only one case. In six

* Submitted for presentation at the Scientific Session of the New York Heart Association, held at The New York Academy of Medicine, April 20, 1960.

others it measured more than 0.10 second, the remaining 30 being in a normal range despite the frequency of the rSR′ configuration in this group.

In the patients with normal right ventricular pressures, the typical electrocardiogram included right deviation of the QRS axis and a prominent R′ in V_1 with a normal QRS duration. As the pressures approached a borderline or minimally elevated range these features of QRS were accentuated, but not strikingly so. More obvious were the T-waves over the right precordium, which became inverted.

In patients with greatly elevated right ventricular pressures, a "systolic overload" pattern of right ventricular hypertrophy appeared. Careful analysis usually revealed these changes as an addition or exaggeration of the typical rSR′ pattern of the normal group. T-wave inversion became extreme, and in those with systolic pressures over 50 mm. Hg., extended over the entire precordium to V_5 and V_6.

T-wave abnormalities are a characteristic component of myocardial hypertrophy and have proved useful in the clinical differentiation between marked and minimal degrees of right ventricular hypertrophy in atrial septal defect.

The Natriuretic Effect of Certain Steroids in Edematous Patients (Abstract)*

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The kidneys, colon, sweat glands and salivary glands of patients with congestive heart failure and cirrhosis of the liver fail to excrete sodium in amounts comparable to that excreted by normal individuals. The accumulation of edema in such instances has been considered to be related to an increased activity of a salt-retaining hormone. An attempt was made to block this hormonal activity by the administration of steroid compounds with structures which, it was hoped, would metabolically compete with this hormone. Since 1951, when this study was begun, 61 steroid compounds have been evaluated for their influence on urinary sodium excretion. Patients with congestive heart failure and cirrhosis of the liver were selected who, on a diet of 50-100 mEq. of sodium, usually excreted less than one mEq. per day. A negligible sodium excretion was a requirement for the test patient so that small increases due to the steroid could be discerned.

Among the 61 compounds studied, five steroid compounds have produced a significant increase in sodium excretion in some patients, namely: Δ^1 allopregnene-21-ol-3, 20-dione acetate, prednisone, and more recently three spirolactones. In one of two trials with Δ^1 allopregnene-21-ol-3, 20-dione acetate, there was a measurable increase in urinary sodium; the maximum was 6 mEq. per day. Urinary sodium increased in four of six trials with prednisone; the maximum was 83 mEq. per day. In ten trials with the spirolactones (SC-8109, SC-8911 and SC-9420, Searle) seven showed increases in urinary sodium, the largest of which was 113 mEq. per day. The effect of these steroids is not sufficiently uniform to accept them at this time as universal diuretics. However, they might well be the point of departure of the search for more useful substances.

* Submitted for presentation at the Scientific Session of the New York Heart Association, held at The New York Academy of Medicine, April 20, 1960.

CORRECTION

In an article entitled "Medical Practice in Colonial America", published in the August 1960 number of the *Bulletin* (vol. 36. No. 8.) the following sentence appears (p. 539): "In this country, the first medical degree was conferred in 1770, by King's College, now the College of Physicians and Surgeons of Columbia University".

A reader, a loyal alumnus of the University of Pennsylvania, has taken exception to this statement and has quoted "a reliable source" which states: "The University of Pennsylvania . . . gave the first medical degree in America in 1768".

The following excerpts are from *"A History of the Medical Department of the University of Pennsylvania"*, by Joseph Carson, Philadelphia, Lindsay and Blakeston, 1869, pp. 66-68.

1) p. 66 "The question as to which medical school, that of Philadelphia or that of New York, the honor of priority is to be awarded in the bestowal of degrees has been a mooted one."

2) p. 67 ". . . in June, 1768, the first Commencement of the College of Philadelphia was held, at which the degree of Bachellor of Medicine was conferred, and further stated that 'at the Commencement of 1771, the degree of M. B. was conferred on seven, and the degree of M.D. on four students'."

3) p. 67-68 ". . . Dr. Morgan [Philadelphia] in writing to Mr. Hewson of London, November 20, 1767, thus expresses himself: '. . . next year [1768] we shall confer the degree of Bachellor in Physic on several of them [students], and that of Doctor in three years after [1771]'."

4) p. 68 "The degree of Bachellor of Medicine was conferred, in 1769, by Kings College, New York, and the degree of Doctor of Medicine in 1770. From this it appears that the claim of priority in conferring degrees in medicine must be awarded to the Philadelphia School, while the precedence in conferring the Doctorate must be given to New York."

Since the sentence in the article to which our reader has taken exception refers to "the first medical degree", it would appear that the above quotations support his contention. (The Editor)

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VOLUME 36

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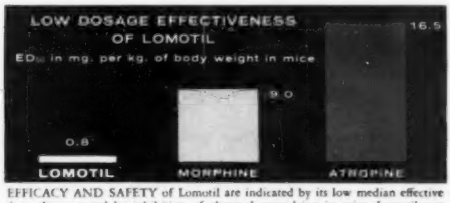

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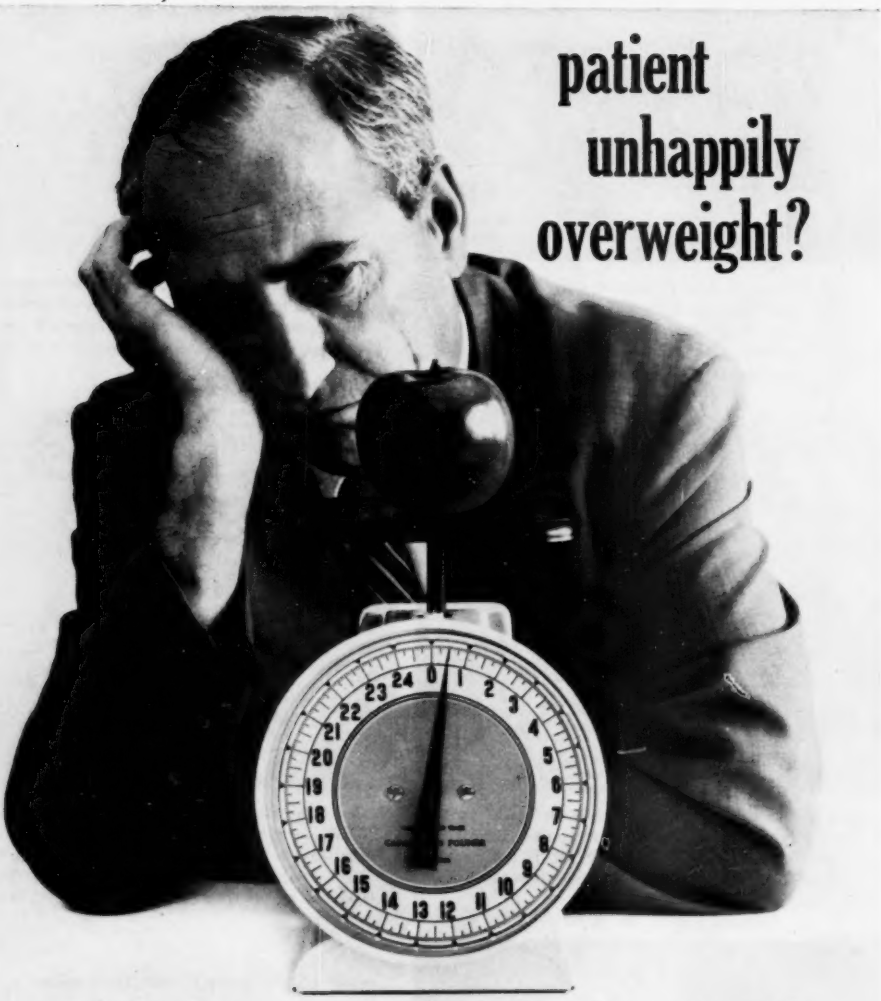

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